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 (佰尔来); 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 (Витаерпавак); *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); J2D279PEM5 (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

the quadrivalent HPV vaccine in women who had been diagnosed and treated for cervical and vulvar or vaginal disease was associated with a 35 to 46% reduction of subsequent HPV related disease (including high grade diseases). The development of therapeutic vaccines would benefit those women already positive for HPV DNA.[9,12] Therapeutic vaccines are based on the viral oncogenic proteins E6 and E7 and are designed to induce cell-mediated immune responses to eliminate infected cells; vaccine candidates are undergoing phase II evaluation. There is also some preliminary study being conducted into the possibility of a 'chimeric' vaccine combining both prophylactic and therapeutic components, but the immunogenicity and efficacy of such vaccines are unknown.

For it to be claimed justifiably that a prophylactic vaccine prevents cervical cancer, it is necessary to show that such a vaccine not only prevents infection but also prevents cancer itself, or at least a defined precursor of disease. Since any placebo-controlled study defining established cancer as an end-point would clearly be unethical, an appropriate compromise is to use the appearance of high-grade dysplasia or pre-cancerous lesions as an end-point, this being regarded as a direct precursor to cervical cancer requiring treatment. However, true pre-cancerous lesions of this kind are relatively unusual in current practice and therefore phase III studies require tens of thousands of subjects in order to establish this efficacy.[3]

Guidance and technical information on HPV, HPV-related diseases, and HPV vaccines has been produced by WHO.[13] They consider HPV vaccines to be highly effective among females not exposed to HPV vaccine genotypes at the time of their first vaccination and that the target group for vaccination will probably be preadolescent girls (about 9 to 12 years of age). Guidelines for the use of HPV vaccine for the prevention of cervical cancer have been developed in the USA by the CDC,[14] the American Cancer Society[15] and the American Academy of Pediatrics (AAP).[16] These authorities recommend routine vaccination for all girls 11 to 12 years of age, although girls as young as 9 years of age may be vaccinated at the discretion of their doctor. Catch-up vaccinations may be given to older girls and young women who have not received or completed a vaccine course. Guidelines have also been developed in the USA[16,17] and Australia[18] for the use of quadrivalent HPV vaccine in males. The CDC and the AAP recommend routine vaccination of males 11 to 12 years of age, although the vaccination series can be started at 9 years of age. Catch-up vaccination courses are recommended for older males aged 13 to 21 years who have not received or completed a vaccine course; males aged 22 to 26 years may also be vaccinated. In the UK the Joint Committee on Vaccination and Immunisation[19] recommends routine vaccination of all girls 12 to 13 years of age. Catch-up vaccination is recommended for girls under 18 years of age.

1. Galloway DA. Papillomavirus vaccines in clinical trials. *Lancet Infect Dis* 2003; 3: 469–75.
2. Lehtinen M, Paavonen J. Effectiveness of preventive human papillomavirus vaccination. *Int J STD AIDS* 2003; 14: 787–92.
3. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; 55: 319–31.
4. Mandic A, Vujkov T. Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? *Ann Oncol* 2004; 15: 197–200.
5. Roden RBS, *et al.* Vaccination to prevent and treat cervical cancer. *Hum Pathol* 2004; 35: 971–82.
6. Lowndes CM, Gill ON. Cervical cancer, human papillomavirus, and vaccination. *BMJ* 2005; 331: 915–16.
7. Harper DM, *et al.* Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004; 364: 1757–65.
8. Poland GA, *et al.* Immunogenicity and reactogenicity of a novel vaccine for human papillomavirus 16: a 2-year randomized controlled clinical trial. *Mayo Clin Proc* 2005; 80: 601–10.
9. Cid-Arregui A. Therapeutic vaccines against human papillomavirus and cervical cancer. *Open Virol J* 2009; 3: 67–83.
10. Paavonen J, *et al.* Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; 374: 301–14. Correction. *ibid.*: 376:1054.
11. Joura EA, *et al.* for the FUTURE I and II Study Group. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* 2012; 344: e1401.
12. Hildesheim A, *et al.* Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA* 2007; 298: 743–53.
13. WHO. *Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals.* Geneva: WHO, 2007. Available at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf (accessed 26/06/07)
14. CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59: 626–9. Correction. *ibid.*: 1184.
15. Saslow D, *et al.* American Cancer Society guidelines for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; 57: 7–28. Also available at: http://caonline.amcancersoc.org/cgi/reprint/57/1/7 (accessed 26/06/07)
16. American Academy of Pediatrics Committee on Infectious Diseases. HPV vaccine recommendations. *Pediatrics* 2012; 129: 602–5. http://pediatrics.aappublications.org/content/129/3/602.full.html (accessed 04/04/12)
17. CDC. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011; 60: 1705–8.
18. Department of Health and Ageing. *The Australian Immunisation Handbook* 10th edition, 2013. Available at: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/EE1905BC65D40BCFCA257B26007FC8CA/$File/part4.pdf (accessed 15/04/13)
19. Health Protection Report. HPV vaccination programme to begin in the UK in Autumn 2008 (issued 2 November, 2008). Available at: http://www.hpa.org.uk/hpr/archives/2007/news2007/news44407.htm (accessed 07/04/08)

Laryngeal papillomatosis. A 5-year-old girl with recurrent laryngeal papillomatosis due to human papillomavirus type 11, who had required frequent surgical treatment, recovered completely after receiving a 3-dose course of quadrivalent human papillomavirus vaccine; the patient was still disease free 17 months after vaccination.[1]

1. Mudry P, *et al.* Recurrent laryngeal papillomatosis: successful treatment with human papillomavirus vaccination. *Arch Dis Child* 2011; 96: 476–7.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Breast feeding. In mothers given the quadrivalent recombinant human papillomavirus vaccine or placebo during clinical studies, the rates of adverse reactions in the mother and in the breast-fed infant, as well as vaccine immunogenicity, were comparable in the 2 groups. Based on apparently the same data the UK licensed product information states that the vaccine can be given to breast-feeding women whereas the US information recommends caution. UK licensed product information for the bivalent vaccine recommends it should only be used when the benefits outweigh the possible risks.

Effects on the nervous system. Demyelinating disease[1-3] and neuromyelitis optica[4] have been temporally associated with human papillomavirus vaccinations, although causality has not been confirmed.

1. Sutton I, *et al.* CNS demyelination and quadrivalent HPV vaccination. *Mult Scler* 2009; 15: 116–19.
2. Álvarez-Soria MJ, *et al.* Trastornos neurológicos desmielinizantes y vacunación del papilomavirus humano. *Rev Neurol* 2011; 52: 472–6.
3. Chang J, *et al.* Demyelinating disease and polyvalent human papilloma virus vaccination. *J Neurol Neurosurg Psychiatry* 2011; 82: 1296–8.
4. Menge T, *et al.* Neuromyelitis optica following human papillomavirus vaccination. *Neurology* 2012; 79: 285–7.

Incidence of adverse effects. Up to September 2009, more than 26 million doses of quadrivalent recombinant human papillomavirus vaccine (qHPV) had been distributed in the USA and 15 037 adverse events after vaccination had been reported to the Vaccine Adverse Event Reporting System (VAERS). Ninety three percent of these reports were considered to be non-serious and 7% serious. Non-serious adverse effects included syncope (sometimes with tonic-clonic movements and other seizure-like activity), pain and swelling at the injection site, dizziness, fever, nausea, headache, hypersensitivity reactions, and urticaria. Serious adverse effects reported after vaccination included Guillain-Barré syndrome, transverse myelitis, pancreatitis, auto-immune disorders, motor neurone disease, and anaphylaxis. Venous thromboembolic events had also been rarely reported; but most people who reported these adverse events had a risk factor, such as the use of an oral contraceptive. There had been 44 deaths reported after vaccination; 27 of which were confirmed and followed up.[1,2]

When compared with other vaccines, most of the adverse effects for qHPV were not more frequent. Furthermore, no unusual pattern or clustering of deaths or serious adverse effects was found that might suggest that the vaccine was responsible.[1,2]

In the UK the bivalent recombinant human papillomavirus vaccine is given as part of the immunisation programme. At the end of July 2009, at least 1.4 million doses had been given and 2195 reports of adverse events after vaccination had been received by the MHRA. The most commonly reported adverse effects were dizziness, headache, nausea, pain in extremity (mainly sore arm), syncope, vomiting, malaise, fatigue, fever, and rash. Other adverse effects reported include 13 reports of chronic fatigue syndrome, 1 report of Guillain-Barré syndrome, and 1 report of facial palsy.[3]

1. Slade BA, *et al.* Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009; 302: 750–7.
2. CDC. Reports of health concerns following HPV vaccination (as updated 5th November 2009). Available at: http://www.cdc.gov/vaccinesafety/Vaccines/HPV/gardasil.html (accessed 23/11/09)
3. MHRA. Human papillomavirus (HPV) immunisation programme—first year safety review. *Drug Safety Update* 2009: 3: 5–8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON059813&RevisionSelectionMethod=LatestReleased (accessed 26/08/10)

Pregnancy. Although specific studies of the quadrivalent and bivalent recombinant human papillomavirus vaccines in pregnant women have not been conducted, some women during clinical development did receive the vaccine in pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in those who received the vaccine and those who received placebo. It is, nevertheless, recommended that vaccination should be postponed until after completion of pregnancy; if pregnancy occurs before the vaccination course has been completed, the remaining doses should be given after pregnancy completion.

These findings and recommendations are supported by a literature review[1] (up to August 2010) that found no increased risk of adverse pregnancy outcomes or malformations for the 369 pregnancies that occurred within 30 days of receiving a human papillomavirus vaccine.

1. Forinash AB, *et al.* Safety of the HPV bivalent and quadrivalent vaccines during pregnancy. *Ann Pharmacother* 2011; 45: 258–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cervarix; Gardasil; *Austral.*: Cervarix; Gardasil; *Austria*: Cervarix; Gardasil; *Belg.*: Cervarix; Gardasil; *Canad.*: Cervarix; Gardasil; *Chile*: Cervarix; Gardasil; *Cz.*: Cervarix; Gardasil; Silgard; *Denm.*: Cervarix; Gardasil; Silgard; *Fr.*: Cervarix; Gardasil; *Ger.*: Cervarix; Gardasil; *Gr.*: Cervarix; Gardasil; *Hong Kong*: Cervarix; Gardasil; *Hung.*: Cervarix; Silgard; *India*: Gardasil; *Indon.*: Cervarix; Gardasil; *Irl.*: Cervarix; Gardasil; Silgard; *Israel*: Cervarix; Gardasil; *Ital.*: Cervarix; Gardasil; *Jpn*: Gardasil; *Malaysia*: Cervarix; Gardasil; *Neth.*: Cervarix; Gardasil; Silgard; *Norw.*: Cervarix†; Gardasil; *NZ*: Cervarix; Gardasil; *Philipp.*: Cervarix; Gardasil; *Pol.*: Cervarix; Gardasil; Silgard; *Port.*: Cervarix; Gardasil; Silgard; *Rus.*: Cervarix (Церварикс); Gardasil (Гардасил); *S.Afr.*: Cervarix; Gardasil; *Singapore*: Cervarix; Gardasil; *Spain*: Cervarix; Gardasil; *Swed.*: Cervarix; Gardasil; *Switz.*: Cervarix; Gardasil; *Thai.*: Cervarix; Gardasil; *Turk.*: Cervarix; Gardasil; *UK*: Cervarix; Gardasil; *Ukr.*: Cervarix (Церварикс); Gardasil (Гардасил); *USA*: Cervarix; Gardasil.

Pharmacopoeial Preparations

Ph. Eur.: Human Papillomavirus Vaccine (rDNA).

Influenza Vaccines

Flu Vaccines; Vacunas de la gripe; Противогриппозные Вакцины.

ATC — J07BB01; J07BB02; J07BB03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Influenza Vaccine (Whole Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Viris Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Split Virion, Inactivated); Vaccinum Influenzae Inactivatum ex Virorum Fragmentis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in embryonated hen eggs and inactivated so that the integrity of the virus particles has been disrupted without diminishing their antigenic properties. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum). A sterile suspension consisting mainly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain

The symbol † denotes a preparation no longer actively marketed

their antigenic properties. The stated amount of haemagglutinin antigen for each strain is usually 15 micrograms per dose. It may contain an adjuvant. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu(adj) may be used on the label as appropriate.

The BP 2014 directs that when Inactivated Influenza Vaccine or Influenza Vaccine is prescribed or demanded and the form is not stated, Influenza Vaccine (Whole Virion, Inactivated), Influenza Vaccine (Split Virion, Inactivated), or Influenza Vaccine (Surface Antigen, Inactivated) may be dispensed or supplied.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Vaccinum Influenzae Inactivatum ex Corticis Antigeniis Praeparatum Virosomale). A sterile aqueous suspension consisting mainly of haemagglutinin and neuraminidase antigens of a suitable strain or strains of influenza virus types A and B either individually or mixed, grown individually in embryonated hen eggs and inactivated so that they retain their antigenic properties and reconstituted to virosomes with phospholipids and without reducing the antigenic properties of the antigens. The stated amount of haemagglutinin antigen for each strain is 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu may be used on the label.

Ph. Eur. 8: (Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Virisque Integris Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu (adj) may be used on the label as appropriate.

Ph. Eur. 8: (Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Vaccinum Influenzae Inactivatum ex Cellulis Corticisque Antigeniis Praeparatum). A sterile aqueous suspension of a suitable strain or strains of influenza virus types A and B, either individually or mixed, grown individually in cell cultures (diploid or continuous cell lines of mammalian origin) and inactivated so that they retain their antigenic properties. It may contain an adjuvant. The stated amount of haemagglutinin antigen for each strain present is usually 15 micrograms per dose. Suitable strains of influenza virus are those recommended by WHO. An antimicrobial preservative may be added. The vaccine should be stored at 2 degrees to 8 degrees, not be allowed to freeze, and be protected from light.

The BP 2014 states that Flu or Flu (adj) may be used on the label as appropriate.

Nomenclature of strains. The strain designation for influenza virus types A, B, and C contains: a description of the antigenic specificity of the nucleoprotein antigen (types A, B, or C) (an internal antigen, the matrix antigen, has also been described); the host of origin (if not man, including, if appropriate, the inanimate source); the geographical origin; the strain number; and the year of isolation; e.g. A/lake water/Wisconsin/1/79. For type A viruses the antigenic description follows (in parentheses) including the antigenic character of the haemagglutinin (e.g. H1) and the antigenic character of the neuraminidase (e.g. N1). There is no provision for describing subtypes of B and C viruses. Recombination between viruses within a type is readily accomplished; the letter R should be added after the strain description to indicate the recombinant nature of the virus, e.g. A/Hong Kong/1/68(H3N2)R. In addition the strain of origin of the H and N antigens of antigenic hybrid recombinant A and B viruses should be given, e.g. A/BEL/42(H1)—Singapore/1/57(N2)R.[1]

1. Assaad FA, *et al.* Revision of the system of nomenclature for influenza viruses: a WHO Memorandum. *Bull WHO* 1980; 58: 585–91.

Uses and Administration

Influenza vaccines are used for active immunisation against seasonal influenza.

Three types of the influenza virus occur, namely types A, B, and C, and the formulation and composition of influenza vaccines is constantly reviewed with changes made to accommodate the antigenic shifts and drifts of the influenza virus. Recommendations concerning the antigenic nature of influenza vaccines are made annually by WHO. Currently, influenza vaccines are mainly of the inactivated type and are available as split-virion vaccines or as various surface-antigen vaccines (including virosomal products); whole-virion vaccines are now seldom used. Live attenuated influenza vaccines against influenza virus types A and B are also available.

Influenza vaccination is generally recommended for persons considered to be at special risk, particularly the elderly, those with chronic heart disease, chronic respiratory disease including asthma (but see Asthma, under Precautions, p. 2395.3), chronic hepatic, neurological, or renal disease, diabetes mellitus, and patients who are immunosuppressed. Vaccination is also recommended for residents, particularly elderly persons and children, in closed institutions. Medical personnel and other persons at risk from infection through contact with infected patients should also receive vaccination. In the USA, annual vaccination of all children from 6 months to 18 years of age and all adults from 50 years of age is recommended. Vaccination usually produces immunity after about 14 days, lasting for about 6 months to 1 year. Injections are therefore scheduled annually so that the period of maximum immunity coincides with the usual period of influenza infection. In the UK and USA, they are generally given between September and early November.

Influenza vaccines are usually given in the UK by deep *subcutaneous* injection or *intramuscular* injection. The preferred site for injection is the deltoid muscle in adults and older children and, in infants and young children, the anterolateral aspect of the thigh. The recommended dose is 0.5 mL for adults and children aged over 3 years. In children aged 6 months to 3 years, doses of 0.25 or 0.5 mL have been used. Children should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time. In the USA, a single intramuscular dose of 0.5 mL of a high-dose inactivated influenza vaccine, containing 60 micrograms per viral strain (180 micrograms per 0.5 mL), may be given for active immunisation of adults 65 years of age and older.

An inactivated *intradermal* seasonal influenza vaccine containing 9 micrograms of antigen per viral strain is available in the UK for use in adults from 18 to 59 years of age and a vaccine with 15 micrograms per viral strain is available for use in adults from 60 years of age; both are given as a single dose of 0.1 mL.

The live attenuated influenza vaccine is given *intranasally*, in a dose of 0.2 mL (0.1 mL in each nostril) in adults (up to 49 years of age) and children from 2 years of age. Children who have not previously been vaccinated against seasonal influenza should be given a second dose at least 4 weeks after the first if receiving the vaccine for the first time.

Current commercially available seasonal influenza vaccines are not effective against avian influenza virus H5N1 but most are effective against pandemic (H1N1) 2009 influenza. For further information on vaccines against these influenza strains, see below.

Reviews.

1. WHO. Influenza vaccines: WHO position paper. *Wkly Epidem Rec* 2005; 80: 279–87. Also available at: http://www.who.int/immunization/wer8033influenza_August2005_position_paper.pdf (accessed 23/6/10)
2. Jefferson T, *et al.* Vaccines for preventing influenza in healthy children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).
3. Audsley JM, Tannock GA. Cell-based influenza vaccines: progress to date. *Drugs* 2008; 68: 1483–91.
4. Goossen GM, *et al.* Influenza vaccination in children being treated with chemotherapy for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 01/12/09).
5. Jefferson T, *et al.* Vaccines for preventing influenza in the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 26/08/10).
6. Jefferson T, *et al.* Vaccines for preventing influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 7. Chichester: John Wiley; 2010 (accessed 26/08/10).
7. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012-13 Influenza Season. *MMWR* 2012; 61: 613–8. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm6132.pdf (accessed 20/09/12)

Avian influenza vaccine. Since 1997, infection of humans with avian influenza virus H5N1 has been reported and is associated with high mortality. Although the current H5N1 influenza strains appear not to be transmissible from human to human, it is of major concern that further mutations or mixing with human influenza strains could convert H5N1 to a strain that would spread from human to human and cause a serious pandemic. Candidate avian influenza vaccines have been investigated and *Sanofi Pasteur, USA* has developed a vaccine (monovalent, split viron, inactivated vaccine containing A/Vietnam/1203/2004 (H5N1) influenza virus strain). Although the vaccine will not be commercially available, it has been licensed by the FDA and will be included in the National Stockpile in the USA for use in the event that the H5N1 virus develops the ability to become readily transmissible from human to human.[1] In the EU, a monovalent, whole viron, vero-cell derived, inactivated vaccine containing the A/Vietnam/1203/2004 (H5N1) influenza virus strain is available (*Vepacel; Baxter, EU*). Targeted use of stockpiled prepandemic influenza vaccines during the pandemic alert period or in the early stages of a pandemic aims to reduce the consequences of an influenza outbreak while specific vaccines against the novel pandemic virus are being developed.[2]

1. FDA. FDA news: FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1 (issued 17th April, 2007). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108892.htm (accessed 26/08/10)
2. Plosker GL. A/H5N1 prepandemic influenza vaccine (whole virion, vero cell-derived, inactivated) [Vepacel]. *Drugs* 2012; 72: 1543–57.

Pandemic (H1N1) 2009 influenza. An influenza outbreak in humans, first detected in Mexico in April 2009 and known as swine flu, was due to a new strain of influenza A virus, subtype H1N1 that transmitted sufficiently easily from person-to-person to be of concern for a pandemic. Infections have been reported worldwide and deaths have occurred: on 11th June 2009 WHO declared a worldwide pandemic. No effective vaccine was immediately available, and an evaluation by the CDC[1] found that vaccination with recent (2005 to 2009) seasonal influenza vaccines was unlikely to provide protection against the pandemic virus.

The first vaccines against this pandemic influenza A strain were approved in September 2009. Methods used to develop and produce these vaccines were similar to those used for seasonal influenza vaccine and the A/California/07/2009 (H1N1) strain of virus was used in their production. The FDA has approved 4 monovalent vaccines; 3 are inactivated and given intramuscularly, while 1 is a live vaccine and is given intranasally. The EMEA has approved 2 monovalent inactivated vaccines containing adjuvants; both are given by intramuscular injection. Guidelines for the use of these vaccines have been developed.[2-4] WHO has recommended that an A/California/07/2009 (H1N1) strain of virus be included in the influenza vaccine for the 2012-2013 northern hemisphere influenza season.[5]

1. CDC. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. *MMWR* 2009; 58: 521–4. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5819.pdf (accessed 22/05/09)
2. National Center for Immunization and Respiratory Diseases, CDC. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2009; 58 (RR-10): 1–8. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5810.pdf (accessed 29/09/09)
3. WHO. WHO recommendations on pandemic (H1N1) 2009 vaccines: pandemic (H1N1) 2009 briefing note 2 (issued 13th July, 2009). Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/index.html (accessed 29/09/09)
4. DoH. Further details about the H1N1 swine flu vaccination programme 2009–2010. Message from the Chief Medical Officer, Sir Liam Donaldson (issued 13th August, 2009). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104315.pdf (accessed 27/08/10)
5. WHO. Recommended composition of influenza virus vaccines for use in the 2012-2013 northern hemisphere influenza season: February 2012. Available at: http://www.who.int/influenza/vaccines/virus/recommendations/201202_recommendation.pdf (accessed 16/03/12)

Adverse Effects

As for vaccines in general, p. 2375.1.

Local and systemic reactions may occur but are usually mild. Fever and malaise sometimes occur and severe febrile reactions have been reported particularly on giving whole-virion vaccine to children, although this type of vaccine is seldom used now. Flu-like symptoms may follow the use of live, attenuated vaccines.

Various neurological syndromes have been temporally associated with use of influenza vaccine, the most notable report being of the Guillain-Barré syndrome occurring after vaccination with inactivated swine influenza vaccine in 1976 (see p. 2395.1).

Effects on the blood. Autoimmune haemolytic anaemia has been reported in two elderly women 2 to 3 days after vaccination with an adjuvanted (MF59) influenza vaccine. Both women were treated with intravenous corticosteroids and other supportive treatment; one women died within 48 hours while the clinical condition of the other improved. The mechanism for this reaction is probably molecular mimicry, although the role of adjuvants cannot be excluded.[1]

1. Montagnani S, *et al.* Autoimmune hemolytic anemia following MF59-adjuvanted influenza vaccine administration: a report of two cases. *Ann Pharmacother* 2011; 45: e8.

Effects on the eyes. For a discussion of bilateral eye redness, occurring as part of an oculorespiratory syndrome after influenza vaccination, see p. 2395.2.

Effects on the nervous system. *BELL'S PALSY.* Between October 2000 and April 2001, the Swiss Drug Monitoring Centre and the University of Zurich received 46 reports of Bell's palsy occurring in patients who had used an inactivated intranasal influenza vaccine (*Nasalflu*). The manufacturers suspended distribution of the vaccine and, after a subsequent study[1] suggested a strong association between the vaccine and the development of Bell's palsy, it was withdrawn from clinical use.

1. Mutsch M, *et al.* Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004; 350: 896–903.

ENCEPHALOMYELITIS SYNDROME. Three cases of acute encephalomyelitis syndrome have been reported in Australia following vaccination with a pandemic (H1N1) 2009 influenza vaccine in previously healthy adults. They were all treated with intravenous methylprednisolone for 3 to 5 days; symptoms improved and weakness resolved in all 3 patients, although, in one patient, the paraesthesia persisted for 3 weeks after treatment.[1]

1. Denholm JT, *et al.* Acute encephalomyelitis syndromes associated with H1N1 09 influenza vaccination. *Neurology* 2010; 75: 2246–8.

GUILLAIN-BARRÉ SYNDROME. In 1976 a limited outbreak of influenza in the USA caused by a virus closely resembling the swine influenza virus led to the use of a killed swine influenza virus vaccine.[1] After about 45 million doses of the vaccine had been given the vaccination programme ceased because there was some evidence of a temporal association between vaccination and the onset of a paralytic polyneuropathy of the Guillain-Barré type. An epidemiologic and clinical evaluation of these cases suggested a definite link between vaccination and the onset of the syndrome with extensive paralysis but no association with the onset of limited motor lesions.

Surveillance systems have since investigated any possible link with the development of Guillain-Barré syndrome. The Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence was inadequate to either accept or reject a causal relationship with non-swine influenza vaccines used after 1976. This review had inspected reports submitted from 1990 to 2003 to VAERS (Vaccine Adverse Events Reporting System in the USA) but considered that such case reports were uninformative with respect to causality, although they were useful for hypothesis generation. One suggestion made by workers monitoring the VAERS data[3] was the question as to whether *Campylobacter* infection could be involved. Influenza vaccines have traditionally been made in chicken eggs. *Campylobacter* is endemic in chickens and a known cause of Guillain-Barré syndrome.

In October 2009, the CDC's Emerging Infections Program began active surveillance to assess the risk for Guillain-Barré syndrome after vaccination with the monovalent unadjuvanted pandemic (H1N1) 2009 influenza vaccine. Preliminary results showed an elevated, statistically significant association between vaccination and Guillain-Barré syndrome. If these findings are confirmed at the end-of-surveillance analysis, the excess risk for Guillain-Barré syndrome (about 0.8 excess cases per 1 million vaccinations) associated with pandemic (H1N1) 2009 influenza vaccine would be comparable to the excess reported for some trivalent seasonal influenza vaccine formulations (about 1 excess case per 1 million vaccinations) and much smaller than the risk seen during the 1976 swine influenza vaccination programme (about 10 excess cases per 1 million vaccinations).[4] From the 1st October until 24th November 2009, 12 possible cases of Guillain-Barré syndrome had been reported to VAERS. After a review of these cases, 4 met Brighton Collaboration criteria for Guillain-Barré syndrome and 4 did not meet the criteria; 4 were still being reviewed.[5] A multinational case-controlled study[6] in 5 European countries reported no increased risk of Guillain-Barré syndrome (after adjusting for flu-like illness and upper respiratory-tract infections) following vaccination with a monovalent adjuvanted pandemic (H1N1) 2009 influenza vaccine.

1. Anonymous. Influenza and the Guillain-Barré syndrome. *Lancet* 1984; ii: 850–1.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)
3. Haber P, *et al.* Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004; 292: 2478–81.
4. CDC. Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. *MMWR* 2010; 59: 657–61.
5. CDC. Safety of influenza A (H1N1) 2009 monovalent vaccines United States, October 1-November 24, 2009. *MMWR* 2009; 58: 1351–6.
6. Dieleman J, *et al.* Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. *BMJ* 2011; 343: d3908.

MULTIPLE SCLEROSIS. Analysis[1] indicated that there was no association between the use in the USA during 1976 of influenza vaccines containing a swine virus component and the development of multiple sclerosis. Later analysis by the Immunization Safety Review Committee in the USA[2] concluded in 2004 that the evidence favoured rejection of a causal relationship between influenza vaccines used in various years (including the swine vaccines of 1976) and relapse of multiple sclerosis but that the evidence was inadequate to either accept or reject a causal relationship with incident multiple sclerosis.

1. Kurland LT, *et al.* Swine flu vaccine and multiple sclerosis. *JAMA* 1984; 251: 2672–5.
2. Stratton K, *et al. Immunization Safety Review: influenza vaccines and neurological complications.* Washington DC: The National Academies Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)

NARCOLEPSY. Cases of narcolepsy, especially in children and adolescents, have been reported following vaccination with monovalent adjuvanted pandemic (H1N1) 2009 influenza vaccines; in most cases *Pandemrix* (manufactured by GlaxoSmithKline) was given.[1-4]

In February 2011, the National Institute for Health and Welfare (THL) of Finland issued a preliminary statement following a retrospective registry-based review into cases of narcolepsy in Finland between 2009 to 2010. A total of 60 cases of narcolepsy were identified in children and adolescents aged 4 to 19 years during this time period and 52 (87%) of them had been vaccinated with *Pandemrix*. The risk of narcolepsy in this age group was calculated to be nine times higher for those vaccinated with *Pandemrix*than for non-vaccinated persons. No increased risk has been seen in those over 19 years of age; no cases were noted in children under 4 years.[2]

In June 2011 the Medical Products Agency (MPA) in Sweden published their results of a review of all cases of severe narcolepsy with cataplexy during 2009 to 2010. Their review also supported a link between vaccination with *Pandemrix* and the risk of narcolepsy in children and adolescents aged 19 years and younger. A total of 81 cases of narcolepsy were identified in children and adolescents during this time period and 69 (85%) of them had been given *Pandemrix* vaccination. Those vaccinated with *Pandemrix* were shown to have an almost 7-fold increased risk for diagnosis of narcolepsy with cataplexy compared with non-vaccinated persons.[3]

The number of cases reported from Sweden, Finland, and Iceland have been higher than for other countries; increased rates of narcolepsy have not been reported from several other European countries, or from Canada where a pandemic (H1N1) 2009 influenza vaccine similar to Pandemrix was used. An increased rate of narcolepsy has also not been reported following use of any other influenza vaccines or for vaccines against other diseases. It does not therefore appear that narcolepsy following vaccination against pandemic influenza is a general worldwide phenomenon and it may be that some unidentified additional factor was operating in Sweden and Finland.[1-4]

Nonetheless, in July 2011, and following a review of the available information, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that *Pandemrix* vaccine should only be given to persons under 20 years of age if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed. Their investigation confirmed an association between *Pandemrix* and narcolepsy and indicated a 6- to 13-fold increased risk of narcolepsy (with or without cataplexy) in vaccinated when compared with unvaccinated children and adolescents; this risk corresponded to about an extra 3 to 7 cases in every 100,000 vaccinated persons.[4]

1. WHO. Global Committee on Vaccine Safety: statement on narcolepsy and vaccination (issued 21st April, 2011). Available at: http://www.who.int/vaccine_safety/topics/influenza/pandemic/h1n1_safety_assessing/narcolepsy_statement/en/ (accessed 21/03/12)
2. National Institute for Health and Welfare. National narcolepsy task force; interim report, 31st January, 2011. Available at: http://www.thl.fi/thl-client/pdfs/dce182fb-651e-48a1-b018-3f774d6d1875 (accessed 21/03/12)
3. Medical Products Agency. Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations — results of a case inventory study by the MPA in Sweden during 2009—2010 (issued 30th June, 2011). Available at: http://www.lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandemrix_110630.pdf (accessed 21/03/12)
4. EMA. Assessment report: Pandemrix. (issued 21st July, 2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000832/WC500118056.pdf (accessed 21/03/12)

Effects on the respiratory tract. For a discussion of respiratory symptoms, occurring as part of an oculorespiratory syndrome after influenza vaccination, see below.

Henoch-Schönlein purpura. Influenza vaccination has been associated with both development[1] and exacerbation[2] of Henoch-Schönlein purpura.

1. Patel U, *et al.* Henoch-Schönlein purpura after influenza vaccination. *BMJ* 1988; 296: 1800.
2. Damjanov I, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; 242: 2555–6.

Oculorespiratory syndrome. During 2000 to 2001, an increased incidence of ocular and respiratory effects was reported in Canada in 960 patients, 96% of whom had received a specific split virion influenza vaccine (*Fluviral S/F*).[1] Symptoms included bilateral redness of the eyes and facial oedema with coughing, wheezing, tightness of the chest, breathing difficulty, or sore throat and were collectively termed oculorespiratory syndrome.[1,2] It was postulated that the syndrome might be due to many microaggregates of unsplit viruses present in the vaccine. A study[3] using an improved formulation of the vaccine found that oculorespiratory symptoms still occurred in 6.3% of recipients and that, since the improved formulation was otherwise minimally reactogenic, such symptoms might be associated with influenza vaccines in general. A subsequent study[4] of influenza vaccination among persons previously afflicted by oculorespiratory syndrome was halted early owing to a 33% rate of recurrence of symptoms within 24 hours. The authors concluded that previously afflicted patients should be warned of the risk of recurrence but that episodes of recurrence were usually mild and well tolerated.[4]

1. National Advisory Committee on Immunization. Supplementary statement for the 2001-2002 season: influenza vaccination of persons who experienced oculo-respiratory syndrome following previous influenza vaccination. *Can Commun Dis Rep* 2001; 27 (Nov.15): 1–7.
2. Boullanne N, *et al.* Clinical manifestations and incidence of oculo-respiratory syndrome following influenza vaccination—Quebec, 2000. *Can Commun Dis Rep* 2001; 27: 85–90.
3. Scheifele DW, *et al.* Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. *Clin Infect Dis* 2003; 36: 850–7.
4. Skowronski DM, *et al.* Randomized, double-blind, placebo-controlled trial to assess the rate of recurrence of oculorespiratory syndrome following influenza vaccination among persons previously affected. *Clin Infect Dis* 2003; 37: 1059–66.

Precautions

As for vaccines in general, p. 2375.2.

Whole-virion influenza vaccine is not recommended for use in children because of the increased risk of febrile reactions. Split-virion and surface-antigen vaccines are, however, suitable for children and infants and are widely used in mass immunisation campaigns. Live, attenuated vaccines should not be given to children and adolescents younger than 18 years of age who are also receiving salicylates because of the association of Reye's syndrome with salicylates and wild-type influenza infection. Salicylates and salicylate-containing products should be avoided for 4 weeks following vaccination.

Recommendations on influenza vaccine use in subjects with egg allergy are discussed below.

Vaccination should be postponed in patients with active infection or acute febrile illness.

Asthma. There have been reports of exacerbations of asthma after influenza vaccination,[1,2] but reviews[3,4] have concluded that evidence of a causal relationship is lacking and that any risk of exacerbation which might exist is outweighed by the risk of influenza itself. Chronic respiratory disease, including asthma, is an indication for influenza vaccination in both the UK and USA. A systematic review has supported the use of inactivated vaccines for patients with chronic obstructive pulmonary disease.[5] A further systematic review, however, has concluded that, while there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination), uncertainty remains about the degree of protection that vaccination affords against asthma exacerbations after influenza infection.[6]

1. Hassan WU, *et al.* Influenza vaccination in asthma. *Lancet* 1992; 339: 194.
2. Nicholson KG, *et al.* Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet* 1998; 351: 326–31.
3. Watson JM, *et al.* Does influenza immunisation cause exacerbations of chronic airflow obstruction or asthma? *Thorax* 1997; 52: 190–4.
4. Park CL, Frank A. Does influenza vaccination exacerbate asthma? *Drug Safety* 1998; 19: 83–8.
5. Poole P, *et al.* Influenza vaccine for patients with chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2006 (accessed 04/05/06).
6. Cates CJ, *et al.* Vaccines for preventing influenza in people with asthma. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2008 (accessed 09/06/08).

Diagnostic tests. False-positive screening enzyme-linked immunosorbent assays (ELISAs) for antibodies to HIV-1, HTLV-1 and hepatitis C virus were reported in blood donors who had recently received influenza vaccine.[1] The reaction was attributed to cross-reactivity of the test kit in use at the time with non-specific IgM.

1. Anonymous. False-positive serologic tests for human T-cell lymphotropic virus type 1 among blood donors following influenza vaccination, 1992. *JAMA* 1993; 269: 2076 and 2078.

Egg allergy. Since most influenza vaccines are grown in cell cultures of chick embryos and may contain residual egg protein (ovalbumin), licensed product information generally contra-indicates their use in individuals with a history of hypersensitivity reactions to egg. However, in recent years, influenza vaccines with a very low ovalbumin content (< 120 nanograms/mL) have become avail-

able and have been used safely in some patients with an allergy to eggs. Egg-free vaccines are also now available.

In the UK, the Department of Health has issued[1] the following advice when immunising subjects with an allergy to eggs:

- subjects with a history of *anaphylaxis to eggs* or with *egg allergy and uncontrolled asthma* should be given an egg-free vaccine or, if unavailable, a vaccine with an ovalbumin content of < 12 nanograms/mL can be given in a hospital setting.
- all other subjects with *allergies to eggs* may be given egg-free vaccine or a vaccine with an ovalbumin content of < 12 nanograms/mL.
- vaccines with ovalbumin content (> 120 nanograms/mL) or where content is not stated should not be given to egg-allergic individuals.

It should be noted that ovalbumin concentrations can vary from season to season and between lots for a given vaccine.

Guidelines for the use of influenza vaccines in persons with a history of egg allergy have also been provided by authorities in the USA.[2]

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=isTIGX (accessed 11/07/12)
2. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR* 2011; **60**: 1128–32. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm6033.pdf (accessed 13/07/12)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies influenza 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

For the effect of influenza vaccination on some other drugs see under Phenobarbital Sodium, p. 538.1, Phenytoin Sodium, p. 545.2, Theophylline Hydrate, p. 1236.3, and Warfarin Sodium, p. 1535.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agrippal; Begrivac; Fluad; Fluarix; Inflexal; Influvac; Isiflu Zonale; Istivac; Mutagrip; Nilgrip; Vaxigrip; *Austral.*: Fluad; Fluarix; Fluvax; Influvac; Intanza; Panvax; Vaxigrip; *Austria*: Addigrip†; Batrevac†; Begrivac†; Fluad; FluVaccinol; Inflexal; Influvac; Intanza; Sandovac; Vaxigrip; *Belg.*: α-Rix; Agrippal†; Fluad; Inflexal†; Influvac S; Intanza; Pandemrix; Vaxigrip; *Braz.*: Agrippal†; Vacina Contra Gripe; Vacina de Virus Inativado Contra Gripe; *Canad.*: Agriflu; Arepanrix; Fluad; FluMist; Fluviral; Influenza A (H1N1) Monovalent Vaccine†; Influvac; Intanza; Vaxigrip; *Chile*: Begrivac; Bio-Flu; Fluarix; Fluazur; Inflexal; Influvac; Mevac-Flu; Vaxigrip; *China*: Agrippal (爱阁力保); Anflu (安尔来福); Fluad (复立达); Fluarix (福禄立适); Fluvax (扶洛凡); Fluviral; Inflexal (因福舒); Influvac (英伏可); Panflu 1 (盼尔来福); Shi Pu Li Er (适普利尔); Vaxigrip (凡尔灵); Ying Pu Ning (英扶宁); Ying Te Fu Lu (英特福禄); Yu Gan Ning (御感宁); *Cz.*: Aflunov; Begrivac; Celvapan; Daronrix; Fluad; Fluarix; Fluenz; Focetria; Foclivia; IDflu; Inflexal†; Influvac; Intanza; Optaflu; Pandemrix; Preflucel; Prepandrix; Pumarix; Vaxigrip; *Denm.*: Agrippal; Begrivac; Fluad; Fluarix; Fluenz; Inflexal; Influvac; Intanza; Mutagrip; Pandemrix†; Vaxigrip; *Fin.*: Agrippal; Begrivac†; Fluarix; Flupar†; Fluvirin†; Inflexal; Influvac; Preflucel; Vaxigrip; *Fr.*: Agrippal; Celvapan†; Fluarix; Fluvirine†; Focetria; Gripguard; Humenza†; Immugrip; Influvac; Intanza†; Mutagrip†; Pandemrix†; Panenza†; Previgrip†; Vaxigrip; *Ger.*: Addigrip†; Afluria; Begrivac†; Fluad; FluVaccinol†; Infectovac Flu; Inflexal†; Influsplit SSW; Influvac; Intanza; Mutagrip; Preflucel; *Gr.*: Addigrip; Agrippal; Evagrip; Fluarix; Inflexal; Influvac; Mutagrip; Vaxigrip; *Hong Kong*: Agrippal; Fluad†; Fluarix; FluMist; Fluvax; Fluzone; Inflexal; Influvac; Intanza; Vaxigrip; *Hung.*: Agrippal; Begrivac; Fluarix; Fluval; IDflu; Influvac; Vaxigrip; *India*: Fluarix; *Indon.*: Agrippal; Fluarix; Vaxigrip; *Irl.*: Addiflu†; Aflunov; Agrippal; Begrivac; Celvapan; Daronrix; Enzira; Fluarix; Focetria; Foclivia; IDflu; Influvac; Intanza; Invivac†; Optaflu; Pandemrix; Preflucel; Prepandemic Influenza Vaccine; Prepandrix; Pumarix; *Israel*: Agrippal; Fluad; Fluarix; FluMist; Fluvirin†; Focetria; Influvac; Pandemrix; Vaxigrip; *Ital.*: Adiugrip; Agrippal; Fluad; Fluarix; Inflexal; Influpozzi; Influvac S; Influvirus†; Isiflu V; Isigrip Zonale; Mutagrip; Vaxigrip; *Malaysia*: Agrippal; Fluarix; Fluvax; Inflexal; Influvac; Vaxigrip; *Mex.*: Agrippal†; Fluarix; Fluzone; *Neth.*: Aflunov; Afluria; Agrippal; Arepanrix†; Batrevac; Celvapan; Daronrix; Fluarix; Fluenz; Fluvax; Fluvirin†; Focetria; Foclivia; IDflu; Inflexal; Influject†; Influvac; Intanza; Invivac†; Mutagrip; Optaflu; Pandemrix; Preflucel; Prepandrix; Pumarix; Vacciflu; Vaxigrip; Vepacel; Xanaflu; *Norw.*: Begrivac†; Celvapan; Fluarix; Influvac; Invivac†; Pandemrix; Preflucel; Vaxigrip; *NZ*: Celvapan; Fluarix; Fluvax; Influvac; Intanza; Panvax; Vaxigrip; *Philipp.*: Agrippal; Fluad†; Fluarix; Inflexal; Influvac; Vaxigrip; *Pol.*: Aflunov; Arepanrix; Begrivac; Celvapan; Daronrix; Fluarix; Focetria; Foclivia; Humenza; IDflu; Inflexal; Influvac; Intanza; Optaflu; Pandemrix; Vaxigrip; *Port.*: Addigrip†; Aflunov; Batrevac†; Celvapan; Chiroflu; Daronrix; Fluad; Fluarix; Fluvirin; Focetria; Foclivia; IDflu; Inflexal; Influvac; Intanza; Invivac; Istivac; Optaflu; Pandemrix; Prepandrix; Vaxigrip; *Rus.*: Agrippal (Агриппал); Begrivac (Бегривак); Fluarix (Флюарикс); Fluvaxin (ФЛЮВАКСИН); Grifor (Грифор); Grippol (Гриппол); Grippovac (Гриппoвак); Inflexal (Инфлексал); Influvac (Инфлювак); MonoGrippol (МоноГриппол); OrniFlu (ОрниФлю); Pandeflu (Пандефлю); Ultravac (Ультравак); *S.Afr.*: Agrippal; Fluarix; Fluvirin†; Influvac; Mutagrip†; Vaxigrip; *Singapore*: Agrippal; Fluad†; Fluarix; Fluvax; Influvac; Intanza; Vaxigrip; *Spain*: Chiroflu; Chiromas; Fluarix; Fluenz; Gripavac†; Influvac; Intanza; Levrison†; Mutagrip; Serinflu†; Vac Antigripal†; Vacuna Antigripal; Vaxigrip; *Swed.*: Afluria; Fluarix; Inflexal; Influvac; Pandemrix; Preflucel; Vaxigrip; *Switz.*: Agrippal; Celtura; Fluad; Fluarix; Focetria; Inflexal; Influvac; Mutagrip; *Thai.*: Agrippal; Begrivac†; Fluad; Fluarix; Fluzone; Inflexal; Influvac; Intanza; Vaxigrip; *Turk.*: Agrippal†; Fluarix; Inflexal; Influvac; Intanza; Vaxigrip; *UK*: Agrippal; Begrivac; Celvapan†; Enzira; Fluarix; Fluenz; Fluvirin; Focetria; Imuvac; Influvac; Intanza; Invivac; Mastaflu†; Optaflu; Pandemrix†; Viroflu; *Ukr.*: Inflexal (Инфлексал)†; Influvac (Инфлювак); *USA*: Afluria; Agriflu†; Fluarix; Flublok; Flucelvax; FluLaval; FluMist; Fluvirin; Fluzone; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; Influenza A (H1N1) Monovalent Vaccine; *Venez.*: Fluarix; Isiflu; Vacuna Purificada.

Homoeopathic Preparations. *Austria*: Globuli gegen Grippe; Metavirulent; *Fr.*: Homeomunil; *Ger.*: metavirulent; *Neth.*: Dolivaxil†; *Switz.*: metavirulent.

Pharmacopoeial Preparations

Ph. Eur.: Inactivated Influenza Vaccine (Split Virion, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated); Influenza Vaccine (Surface Antigen, Inactivated, Prepared in Cell Cultures); Influenza Vaccine (Surface Antigen, Inactivated, Virosome); Influenza Vaccine (Whole Virion, Inactivated); Influenza Vaccine (Whole Virion, Inactivated, Prepared in Cell Cultures).

Japanese Encephalitis Vaccines

Vacunas de la encefalitis japonesa.

ATC — J07BA02.

Uses and Administration

Two types of inactivated Japanese encephalitis (JE) vaccine containing either the Nakayama or the Beijing-1 strain of the virus and grown in mouse-brain tissue have generally been used for active immunisation against encephalitis due to JE virus. The Nakayama strain vaccine produced in Japan was widely available internationally, but production has been stopped. Another inactivated JE vaccine is made in China from the Beijing-3 strain of JE virus and grown in Syrian hamster kidney-cell cultures. This vaccine has been replaced in the Chinese vaccination programme by a live, attenuated JE virus (strain SA 14-14-2) vaccine that is also produced on primary hamster cells. Most recently the vaccine IC-51 (an inactivated, adsorbed JE vaccine also based on the strain SA 14-14-2, and manufactured in cultivated Vero cells) has been approved for use in several countries. JE vaccines are widely used in China, Japan and other parts of Asia where JE is endemic and may form part of the WHO Expanded Programme on Immunization. Vaccination is recommended for visitors to rural areas of South East Asia and the Far East where infection is endemic and where the visit is to be for more than one month; it is also recommended for shorter visits in individuals likely to be at exceptional risk.

In the UK, two inactivated JE vaccines are available; one containing Nakayama strain grown in mouse brain and the other manufactured in cultivated Vero cells.

Children from 1 year of age to under 3 years of age who are non-immune travellers may be given 3 doses each of 0.5 mL of inactivated *mouse-brain vaccine* subcutaneously at 0, 7 to 14, and 28 to 30 days. Children from 3 to 17 years of age may be given 3 doses each of 1 mL; full immunity will take up to one month to develop after the last dose. An abbreviated dosage schedule has been suggested (for those aged 3 to 17 years) if time is not available for this standard schedule: two doses at 0 and 7 to 14 days *or* 3 doses at 0, 7, and 14 days may be given. A booster dose should be given 12 months after the primary immunisation course and then at 3-year intervals.

Infants and children from 2 months to under 3 years of age may be given 2 doses each of 0.25 mL of the inactivated *Vero cell vaccine* intramuscularly at 0 and 28 days. Children from 3 years of age and adults may be given 2 doses each of 0.5 mL; full immunity will take up to one week to develop after the last dose. A booster dose should be given to adults 12 to 24 months after the primary immunisation course, before potential re-exposure to JE virus. Those at continuous risk for acquiring Japanese encephalitis should receive a booster dose at month 12 after primary immunisation.

In the USA an inactivated vaccine manufactured in cultivated Vero cells is available. It is licensed for use in adults (or from the age of 17 years); the vaccination schedule is similar to that used in the UK. For those less than 17 years of age, the CDC recommends enrolment in an ongoing clinical study, giving the inactivated Vero cell vaccine off-label, or obtaining a vaccine at an international travellers' clinic in Asia.

In areas where JE is endemic, primary immunisation with inactivated vaccines has been given according to a different schedule. Although the ages and schedule of subsequent boosters varies in different countries, the same schedule is used for primary immunisation. The first dose is given at age 6 months to 3 years according to the country, but in all cases is followed by a second dose 1 to 4 weeks later and then a third after 1 year. Live attenuated Japanese encephalitis vaccines are also used, in single or 2-dose schedules (see below), in some countries in the Far East where disease is endemic.

Guidelines and recommendations.

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Inactivated Japanese encephalitis vaccines grown in mouse-brain tissue have been widely used in Asia for some years. In Japan, the incidence of the disease has decreased since the introduction of nationwide vaccination in the mid-1960s. Recently another inactivated vaccine, IC-51, based on the strain SA 14-14-2 and manufactured in cultivated Vero cells, has been approved for use.[1-4]

A live attenuated vaccine, SA14-14-2, is widely used in China and is replacing the use of inactivated vaccine. Studies[5,6] with the live attenuated vaccine showed that 2 doses given a year apart were 97% effective in an endemic region of rural China. Similar results were obtained when the interval between doses was reduced to 1 to 3 months. A further case-control study[7] in Nepal found that single-dose administration was more than 99% effective.

Other vaccines are under development including recombinant DNA and chimeric vaccines. Recombinant vaccines delivered using poxvirus vectors were also investigated but research appears to have been halted.[8]

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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Hypersensitivity reactions including urticaria, angioedema, hypotension, and dyspnoea have been reported mainly in travellers from non-endemic areas. In May 2005 the Japanese government suspended routine vaccination with mouse brain-derived vaccine in response to a report of acute disseminated encephalomyelitis after vaccination; however, a causal link has not been established.

Persons with unstable neurological conditions, including convulsions in the past year, may be at higher risk of adverse events. It is suggested that vaccine should not be given to those who are recovering from acute disseminated encephalomyelitis or to those with Guillain-Barré syndrome, multiple sclerosis, or other demyelinating disorders.

The IC-51 vaccine, which is manufactured in cultured Vero cells and contains no gelatin or animal protein, should theoretically reduce the potential for hypersensitivity and neurological reactions.

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Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: JE-Vax†; Jespect; *Austria*: Ixiaro; *Belg.*: Ixiaro; *Canad.*: Ixiaro; JE-Vax†; *China*: Ai Pu Sheng (爱普生); An Kang (安康); Jieyiwei (杰益维); Cz.: Ixiaro; *Denm.*: Ixiaro; *Fr.*: Ixiaro; *Ger.*: Ixiaro; *India*: Jencevac; *Irl.*: Ixiaro; *Israel*: Ixiaro; *Jpn*: Encevac; Jebik V; *Neth.*: Ixiaro; *Norw.*: Ixiaro; *NZ*: Jespect; *Pol.*: Ixiaro; *Port.*: Ixiaro; *Spain*: Ixiaro; *Swed.*: Ixiaro; *Switz.*: Ixiaro; *Thai.*: CD Jevax; JE-Vaccine†; *UK*: Ixiaro; *USA*: Ixiaro; JE-Vax†.

Jellyfish Venom Antisera

Antídoto contra las picaduras de medusa; Antisuero contra el veneno de la medusa; Jellyfish Antivenins; Jellyfish Antivenoms.

Uses and Administration

An antiserum for use in the management of severe stings by the box jellyfish or sea wasp *Chironex fleckeri* is available in Australia. The preparation contains the specific antitoxic globulins that neutralise the venom of *Chironex fleckeri* and is prepared from the serum of sheep immunised with the venom of the box jellyfish.

Box jellyfish antivenom is usually given by the intravenous route in a dose of 20 000 units. Alternatively, 60 000 units may be injected intramuscularly.

Jellyfish stings. Many stings caused by the box jellyfish *Chironex fleckeri* are of little consequence and can be managed by simple first aid measures; however, some can be rapidly fatal so immediate assessment is vital.[1] Fragments of tentacle adhering to the skin should be inactivated by the application of vinegar or 3 to 10% acetic acid solution. Cardiopulmonary resuscitation may be necessary in severe cases. The antiserum can be effective if given quickly and in adequate dosage,[2,3] although use is mainly reserved for those with cardiorespiratory instability, severe pain refractory to opioid analgesics, or at risk of significant scarring.[1,3] Some experimental evidence suggested that verapamil might be useful for treatment of the cardiotoxic effects of the venom and allow more time for the antiserum to exert its action,[1,4] but it is now considered to be contra-indicated.[3] Some have suggested that the *Chironex fleckeri* antiserum may be effective for severe envenomation by related species.[3,5]

Irukandji syndrome consists of several hypercatecholaminergic symptoms (such as generalised pain, distress, hypertension, cardiomyopathy, and pulmonary oedema) arising from envenomation with the small box jellyfish *Carukia barnesi*.[1,6,7] Treatment is essentially symptomatic and supportive. The *Chironex fleckeri* antivenom is not effective.[3,5,7] Acetic acid may also be helpful for stings by related species (see p. 2427.1).

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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Leishmaniasis Vaccines

Vacunas de la leishmaniasis.

Profile

Vaccines containing *Leishmania* spp. are under investigation in an attempt to prevent cutaneous leishmaniasis.

The inoculation of an infective strain of a *Leishmania* sp. into the skin, a technique known as leishmanisation, has been used to protect against cutaneous leishmaniasis (p. 922.1). Although the technique has been standardised it is not generally recommended since large, slow-healing lesions have occurred in some patients. There is currently no effective vaccine for any form of leishmaniasis. First-generation vaccines containing killed leishmanial promastigotes, with or without BCG as an adjuvant, have been developed and tested in humans. These have conferred some protection against cutaneous disease but it has waned relatively quickly in some cases. They have not been found to confer protection against visceral leishmaniasis (p. 923.1). Studies are ongoing investigating the use of alum as an adjuvant. There is also further investigation into second-generation vaccines using different approaches such as the use of surface antigens (gp63 and lipophosphoglycan), promastigote antigen from *L. amazonensis*, enzyme receptor (LACK), Th1-driving adjuvant such as interleukin-12, oligodeoxynucleotides with leishmanial antigens, or recombinant leishmanial antigen (TSA, LmSTI-1), all of which have conferred some protection in *mice*. A glycoprotein-enriched *L. donovani* promastigote vaccine (*Leishmune*) is available for prophylactic veterinary use in Brazil. DNA constructs encoding gp63 and LACK have also conferred protection against *L. major* in *mice*. A chimeric vaccine has also been developed combining three leishmanial antigens (LeIF, LmSTI-1, and TSA) in monophosphoryl lipid A adjuvant but had, at best, mixed results in studies in *dogs*. Attenuated vaccines prepared by gene deletion have shown promise in *mice*. The saliva of sandflies (the vector) seems to enhance infectivity, and vaccines against salivary or gut antigens of the insect have also been investigated.

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Leprosy Vaccines

Vacunas de la lepra.

Profile

Vaccines against leprosy including those using *Mycobacterium leprae*, as well as other mycobacteria, are under investigation. A killed vaccine has been developed in India for use as an adjunct to standard multidrug therapy in the treatment of leprosy. Although studies of new vaccines are continuing, BCG vaccine (p. 2378.3) also appears to be effective.

Leprosy vaccines are being studied both to prevent infection with *M. leprae* (immunoprophylaxis) and to prevent disease in infected individuals (immunotherapeutic). Attempts to develop a vaccine against leprosy are based on the assumption that induction of a cell-mediated immune response to *Mycobacterium leprae* will lead to protection against the bacillus. Several vaccines have been studied and include BCG, BCG plus heat-killed *M. leprae*, heat-killed *Mycobacterium w*, and ICRC (Indian Cancer Research Centre) bacillus. The fortuitous finding that BCG vaccine, which is inexpensive and widely available, is effective against leprosy has important implications for leprosy control. Considerable **immunoprophylaxis** against leprosy is afforded by BCG vaccination (see p. 2378.3), and a study in Malawi showed that repeated vaccination provided additional protection.[1] However, the addition of killed *M. leprae* did not produce any further improvement, confirming preliminary results of a study in Venezuela.[2] However, in a report of their sixth meeting,[3] the WHO Technical Advisory Group on the Elimination of Leprosy reported superior vaccine efficacy for BCG plus heat-killed *M. leprae* than with BCG alone in a prophylactic leprosy vaccine study in south India. The study was begun in 1991 and involved 171 400 subjects who received either BCG alone, BCG plus heat-killed *M. leprae*, *Mycobacterium w*, ICRC bacillus, or placebo. Three surveys of the results have since been conducted by way of follow-up; the preliminary findings of the latest of these surveys revealed that the overall efficacy rates for the vaccines were 22% for BCG alone, 67% for BCG plus heat-killed *M.leprae*, 41% for *Mycobacterium w*, and 51% for ICRC bacillus. Within these results, the findings specifically for efficacy in contacts of patients with leprosy were 11% for BCG alone, 88% for BCG plus heat-killed *M. leprae*, 87% for *Mycobacterium w*, and 11% for ICRC bacillus. Further studies are being conducted in Brazil regarding the use of BCG for booster doses in schoolchildren, and also for its use in household contacts. There is also evidence that combining BCG vaccination with rifampicin chemoprophylaxis produces additive benefit.[4]

Beneficial responses have been reported[5-11] from the **immunotherapeutic** use of *Mycobacterium w* vaccine with standard multidrug therapy (p. 188.3) although a small increase in Type 1 lepra reactions has been seen.[10-12] A similar, and possibly identical, vaccine based on the ICRC bacillus has also been evaluated.[13,14] Immunotherapy with BCG and heat killed *M.leprae* has produced beneficial responses when given as an adjunct to chemotherapy.[15] WHO has suggested that the immunotherapeutic use of vaccines may ultimately prove to be more clinically relevant than the immunoprophylactic use,[13] and high compliance with immunotherapy appears to be attainable.[16]

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16. Walia R, *et al.* Field trials on the use of Mycobacterium w vaccine in conjunction with multidrug therapy in leprosy patients for immunotherapeutic and immunoprophylactic purposes. *Lepr Rev* 1993; 64: 302–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Immuvac.

Leptospirosis Vaccines

Leptospira Vaccines; Vacunas de la leptospirosis.

Profile

Leptospirosis vaccines prepared from killed *Leptospira interrogans* are available in some countries. They are used for active immunisation against leptospirosis icterohaemorrhagica (spirochaetal jaundice; Weil's disease) in persons at high risk of contracting the disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Spirolept.

Lyme Disease Vaccines

Vacunas de la enfermedad de Lyme.

Profile

Vaccines based on recombinant outer surface proteins of *Borrelia burgdorferi* were developed and used in some countries for active immunisation against Lyme disease in persons at risk of contracting the disease.

Lyme arthritis refractory to treatment with antibacterials has occurred rarely as an immune reaction to vaccine-derived outer surface proteins of *Borrelia burgdorferi*.

Malaria Vaccines

Vacunas de la malaria; Vacunas del paludismo.

Profile

Malaria vaccines acting against the sporozoite, asexual, and sexual stages of the *Plasmodium falciparum* life cycle are under investigation, as well as multicomponent vaccines consisting of combined antigens from various stages.

Vaccine development. Chemoprophylaxis of malaria is becoming increasingly problematical (see p. 644.1), resulting in the increased desirability of effective malaria vaccines, several of which have been, or are being, studied clinically. The various approaches to malaria vaccine development have been extensively reviewed.[1-15] Malaria vaccines can be categorised into 4 main groups:

- vaccines against pre-erythrocytic forms of the parasite, specifically the sporozoite and liver stages of infection. A sporozoite vaccine could prevent infection either via an antibody response to block invasion of liver cells or via a cell-mediated response to destroy infected liver cells by preventing release of parasites into the bloodstream. The most advanced of these vaccines are derived from the circumsporozoite antigen present on the sporozoite and the main vaccine candidate of this type is RTS,S. This vaccine is comprised of the antigenic C-terminus of the circumsporozoite gene from *Plasmodium falciparum* fused to hepatitis B surface antigen and formulated with different adjuvants. Encouraging results in early studies in endemic African areas have been reported with the variants RTS,S/AS02A,[16] RTS,S/AS02D,[17] and RTS,S/AS01E.[18] The US military is also investigating the possibility of DNA vaccines for malaria, including a liver-stage DNA candidate encoding the circumsporozoite (CS) protein of *P. falciparum*; however, this vaccine has so far failed to induce antigen-specific antibodies. A multiple-antigen version of this DNA vaccine, known as MuStDo5, encoding 5 different liver-stage antigens including CS is also under investigation. Some workers are investigating the prospect of priming with a DNA vaccine and boosting with recombinant antigen or viral vectors. There is also some development of vaccines that focus on the intracellular liver stage of the parasite, since some antigens expressed by sporozoites or merozoites can also be expressed by liver stage parasites
- vaccines against asexual erythrocytic stages, directed at the merozoite form of the parasite. These vaccines would be expected to reduce the severity and the duration of disease by decreasing the blood-parasite density; this effect correlates with reduced symptoms and risk of death. The most advanced asexual vaccine candidate is merozoite surface protein 1 (MSP-1), which forms part of a complex thought to be involved in erythrocyte invasion; antibodies to MSP-1 have been shown to block parasite entry to erythrocytes *in vitro*. Recombinant MSP-1 has also been shown to protect against lethal parasite challenge in *animal* studies. Several other merozoite surface proteins are also under development (MSP-2, 3, 4, 5, 8, and 9). A vaccine comprising MSP-1 and MSP-2 plus *P. falciparum* ring-infected erythrocyte (RESA) has recently shown a 62% reduction in parasite density in children in a study in Papua New Guinea. Two further promising asexual erythrocytic stage vaccine candidates are the apical membrane antigen-1 (AMA-1) and erythrocyte-binding antigen-175 (EBA-175)
- transmission-blocking vaccines to raise antibodies in humans against the gamete stage of the parasite present in the mosquito gut; these antibodies would then be taken up by the biting mosquito from in the blood and block further parasite development in the mosquito, thus rendering it non-infectious. Blocking transmission in this way could reduce infectivity of mosquitoes in that they would carry fewer parasites, and could extend the useful life of a pre-erythrocytic or erythrocytic vaccine by preventing transmission of antibody-resistant mutants. The most advanced candidate vaccines of this type contain the *P. falciparum* surface protein antigens Pfs-25 and Pfs-28 or the *P. vivax* homologues Pvs-25 and Pvs-28. Recombinant forms of these antigens are currently being investigated. Other similar sexual stage vaccines under development include Pfs-48/45 and Pfs-230
- vaccines against the toxins produced by the parasite that contribute to the disease itself. The glycosylphosphatidyl inositol (GPI) anchor, which binds several of the parasite's antigens to the erythrocyte membrane, has been shown to be highly toxic in *mouse* models, but has potential for disease attenuation if it can be detoxified and rendered safe.

A multi-antigen, multistage combination vaccine is thought to be the best approach to effective vaccination against malaria. One such vaccine, SPf66, a synthetic preparation of three antigens from the asexual phase of the parasite in the blood linked by a sporozoite antigen has been studied but little or no evidence for its protective efficacy has been found.[3] Another multicomponent vaccine, NYVAC-Pf7, using a recombinant vaccinia viral vector that expresses 7 proteins from different stages of malarial infection, has also been studied,[19] but results have been disappointing. A further multicomponent vaccine, CDC/NIIMALVAC-1 has provided encouraging preliminary results in *animals* and *in vitro*.[20]

1. Webster D, Hill AVS. Progress with new malaria vaccines. *Bull WHO* 2003; 81: 902–9.
2. Moorthy VS, *et al.* Malaria vaccine developments. *Lancet* 2004; 363: 150–6.
3. Graves PM, Gelband H. Vaccines for preventing malaria (SPf66). Available in The Cochrane Library; Issue 2. Chichester: John Wiley; 2006.
4. WHO. State of the art of new vaccines: research & development (January 2005). Available at: http://www.who.int/vaccine_research/documents/Dip%20814.pdf (accessed 27/08/10)
5. Graves PM, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
6. Graves PM, Gelband H. Vaccines for preventing malaria (blood-stage). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 10/06/08).
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9. Mikolajczak SA, *et al.* Preerythrocytic malaria vaccine development. *Curr Opin Infect Dis* 2007; 20: 461–6. Correction. *ibid.*: 656.
10. Genton B, Reed ZH. Asexual blood-stage malaria vaccine development: facing the challenges. *Curr Opin Infect Dis* 2007; 20: 467–75.
11. Saul A. Mosquito stage, transmission blocking vaccines for malaria. *Curr Opin Infect Dis* 2007; 20: 476–81.
12. Sharma S, Pathak S. Malaria vaccine: a current perspective. *J Vector Borne Dis* 2008; 45: 1–20.
13. Vekemans J, Ballou WR. Plasmodium falciparum malaria vaccines in development. *Expert Rev Vaccines* 2008; 7: 223–40.
14. Pinzon-Charry A, Good MF. Malaria vaccines: the case for a whole-organism approach. *Expert Opin Biol Ther* 2008; 8: 441–8.
15. Tyagi RK, *et al.* Various carrier system(s)-mediated genetic vaccination strategies against malaria. *Expert Rev Vaccines* 2008; 7: 499–520.
16. Alonso PL, *et al.* Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *Lancet* 2005; 366: 2012–12.
17. Abdulla S, *et al.* Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* 2008; 359: 2533–44.
18. Bejon P, *et al.* Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. *N Engl J Med* 2008; 359: 2521–32.
19. Ockenhouse CP, *et al.* Phase I/IIa safety, immunogenicity, and efficacy trial of NYVAC-Pf7, a pox-vectored, multiantigen, multistage vaccine candidate for Plasmodium falciparum malaria. *J Infect Dis* 1998; 177: 1664–73.
20. Shi YP, *et al.* Immunogenicity and in vitro protective efficacy of a recombinant multistage Plasmodium falciparum candidate vaccine. *Proc Natl Acad Sci U S A* 1999; 96: 1615–20.

Measles Immunoglobulins

Inmunoglobulinas contra el sarampión.

ATC — J06BB14.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Measles Immunoglobulin; Immunoglobulinum Humanum Morbillicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the measles virus. Normal immunoglobulin may be added. It contains not less than 50 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Uses and Administration

Measles immunoglobulins may be used for passive immunisation against measles. They have been used to prevent or modify measles in susceptible persons who have been exposed to infection; in the UK, normal immunoglobulin is usually given.

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. *Gr.*: Moruman.

Pharmacopoeial Preparations

Ph. Eur.: Human Measles Immunoglobulin.

Measles Vaccines

Vacunas del sarampión.

ATC — J07BD01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles Vaccine (Live); Vaccinum Morbillorum Vivum). A freeze-dried preparation of a suitable live attenuated strain of measles virus grown in cultures of chick-embryo cells or human diploid cells. It is prepared immediately before use by reconstitution from the dried vaccine. The virus concentration is not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Measles may be used on the label.

Uses and Administration

Measles vaccines are used for active immunisation against measles. Measles strains currently used in vaccines are usually the more attenuated Enders' attenuated Edmonston strain or the Schwarz strain. A high-potency measles vaccine prepared from the Edmonston-Zagreb strain of measles virus was formerly used but was stopped because of evidence of increased mortality (see High-titre Vaccines and Mortality, under Adverse Effects, p. 2399.2).

For primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see below.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response. However, they have been given to infants at 6 to 9 months of age in developing countries and in the USA in certain circumstances (such as during measles outbreaks) (see also Immunisation Schedules, below).

Single-antigen measles vaccines have also been used for prophylaxis after exposure to measles provided they are given within 72 hours of contact.

Administration. Several alternative routes of administration of measles vaccines have been investigated in an attempt to overcome some of the disadvantages of subcutaneous or intramuscular injection.[1] Aerosol administration has produced good responses in children over 9 months of age, although this route was not so effective in younger children.[2,3] Aerosol administration could be potentially useful for mass immunisation campaigns, a suggestion confirmed in a randomised study.[4]

Oral vaccines against measles, produced in edible plants, are under investigation.[5,6]

Work is currently underway to develop oral and/or nasal vaccines that will be suitable in infants less than 9 months of age, a time when they are vulnerable due to waning maternal antibodies.

1. Cutts FT, *et al.* Alternative routes of measles immunization: a review. *Biologicals* 1997; 25: 323–38.
2. Hiremath GS, Omer SB. A meta-analysis of studies comparing the respiratory route with the subcutaneous route of measles vaccine administration. *Hum Vaccin* 2005; 1: 30–6.
3. Low N, *et al.* Immunogenicity and safety of aerosolized measles vaccine: systematic review and meta-analysis. *Vaccine* 2008; 26: 383–98.
4. Dilraj A, *et al.* Response to different measles vaccine strains given by aerosol and subcutaneous routes to schoolchildren: a randomised trial. *Lancet* 2000; 355: 798–803.
5. Webster DE, *et al.* Appetising solutions: an edible vaccine for measles. *Med J Aust* 2002; 176: 434–7.
6. Muller CP, *et al.* Immunogenic measles antigens expressed in plants: role as an edible vaccine for adults. *Vaccine* 2003; 21: 816–19. Correction. *ibid.*: 3093.

Immunisation schedules. In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. As a result of concern that measles vaccine would not elicit an appropriate immune response in young infants due to the persistence of maternal antibodies in circulation, vaccination has generally not been attempted in children under 12 months old. However, infants born to vaccinated mothers tend to have lower levels of maternal antibodies and are susceptible to measles infection at under 12 months of age; vaccination has been shown to be effective at 6 to 9 months of age in such children,[1-3] although antibody titres were lower in infants vaccinated at 6 months of age than in those vaccinated later.[1,4]

In the UK and USA, routine vaccination is given at between 12 and 15 months, with a second dose given at between 4 and 6 years (see the immunisation schedules summarised under Vaccines, p. 2373.3). Similar schedules are used in other countries. There is evidence that these 2-dose strategies will produce high levels of immunity in the community. During an outbreak of measles, vaccination may be given as early as 6 months of age;[5] revaccination is recommended in any child who is vaccinated before their first birthday. Vaccine may be given to non-immune persons of any age considered to be at risk of infection even if their immune status is uncertain.

For discussion of immunisation schedules in the developing world, see under Expanded Programme on Immunization, below.

1. Johnson CE, *et al.* Measles vaccine immunogenicity in 6- versus 15-month-old infants born to mothers in the measles vaccine era. *Pediatrics* 1994; 93: 939–44.
2. Carson MM, *et al.* Measles vaccination of infants in a well-vaccinated population. *Pediatr Infect Dis J* 1995; 14: 17–22.
3. Markowitz LE, *et al.* Changing levels of measles antibody titers in women and children in the United States: impact on response to vaccination. *Pediatrics* 1996; 97: 53–8.
4. Gans HA, *et al.* Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 1998; 280: 527–32.
5. De Serres G, *et al.* Effectiveness of vaccination at 6 to 11 months of age during an outbreak of measles. *Pediatrics* 1996; 97: 232–5.

EXPANDED PROGRAMME ON IMMUNIZATION. Measles remains a leading cause of death among young children, despite the availability of a safe and effective vaccine for the past 40 years. WHO estimated 454 000 people, the majority of them children, died from measles and measles complications in 2004.

In the developed world measles vaccine (usually as measles, mumps, and rubella vaccine) is usually given in the second year of life. If given earlier, passively-acquired maternal antibodies against measles may interfere with development of protective immunity.

In the developing world, protection given by maternal antibodies is often rapidly lost and in hyperendemic areas, such as urban and peri-urban areas, clinical measles may occur in children as young as 5 to 6 months of age. Immunisation against measles is part of WHO's Expanded Programme on Immunization (see, p. 2374.2). The first dose of measles vaccine is given to children at the age of 9 months or shortly thereafter. A 'second opportunity' for immunisation is provided to all children (either through routine immunisation campaigns or by targeted supplementary activities depending on local need). This assures measles immunity in children who failed to receive a previous dose of measles vaccine, as well as in those who were vaccinated but failed to develop immunity following vaccination (about 10 to 15% of those children vaccinated at 9 months of age).

References.

1. 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 03/03/10)

Immunisation for travellers. WHO recommends that all travellers who have not been immunised should be offered measles vaccine. Infants who are travelling to areas where measles is highly endemic may receive a dose at the age of 6 months but those who receive the first dose of measles vaccine between the ages of 6 to 8 months should also receive the scheduled primary immunisation doses later.[1]

It is generally recommended that individuals with at least a moderate degree of immune deficiency should receive measles vaccine even when travelling to areas with a low risk of contracting the disease.[1]

1. WHO. *International travel and health* 2010 ed. Available at: http://www.who.int/entity/ith/ITH2010.pdf (accessed 27/08/10)

Adverse Effects

As for vaccines in general, p. 2375.1.

Fever and rashes may occur after measles vaccines. The fever generally starts about 1 week after the injection, lasts for about 2 or 3 days, and has sometimes been accompanied by convulsions. More serious effects reported rarely include encephalitis and thrombocytopenia.

Reviews.

1. Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Safety* 1998; 19: 435–54.

Incidence of adverse effects. Some brief comments made by the Advisory Committee on Immunization Practices in the USA on adverse effects of standard measles vaccines.[1] An excellent safety record of measles vaccines has been indicated by the experience gained through the use of more than 240 million doses up to 1993. Fever with a temperature of 39.4 degrees or more may develop in 5 to 15% of vaccinees beginning 5-12 days after vaccination and usually lasts several days. Transient rashes have been reported in about 5% of vaccinees. CNS disorders, including encephalitis and encephalopathy, have been reported with a frequency of less than one case per million doses given. The incidence of encephalitis or encephalopathy after vaccination is lower than the incidence rate of encephalitis of unknown origin suggesting that such events after vaccination may be only temporally related to, rather than due to, vaccination.

1. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; 45 (RR 12): 1–35.

Atypical measles. The atypical-measles syndrome has occurred in persons vaccinated against measles and later exposed to the natural infection. The syndrome has been characterised by high fever and atypical rash; abdominal pain has been common and pneumonia almost universal.[1] Although atypical measles has occurred particularly in patients given killed vaccine[1] (no longer used) it has been reported in recipients of live measles vaccines.[2,3]

Measles occurring in patients previously vaccinated with live measles vaccines may be mild and go unrecognised. However, secondary vaccine failure does not appear to be a major problem (see Immunisation Schedules under Uses, p. 2398.3).

1. Anonymous. The atypical-measles syndrome. *Lancet* 1979; i: 962–3.
2. Chatterji M, Mankad V. Failure of attenuated viral vaccine in prevention of atypical measles. *JAMA* 1977; 238: 2635.
3. Henderson JAM, Hammond DI. Delayed diagnosis in atypical measles syndrome. *Can Med Assoc J* 1985; 133: 211–13.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with monovalent measles vaccine or other measles-containing vaccines, see under Measles, Mumps and Rubella Vaccines, p. 2400.3.

Effects on the nervous system. *GUILLAIN-BARRÉ SYNDROME.* No association was found between measles vaccination and Guillain-Barré syndrome in an analysis of 2296 cases.[1]

1. da Silveira CM, *et al.* Measles vaccination and Guillain-Barré syndrome. *Lancet* 1997; 349: 14–16.

OPTIC NEURITIS. For a report of optic neuritis in 2 children after being given measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p. 2400.1.

SUBACUTE SCLEROSING PANENCEPHALITIS. Subacute sclerosing panencephalitis (SSPE) is a rare complication of measles infection (p. 961.2) and has been reported in children who have received measles vaccine but have no history of clinical disease. Nevertheless mass measles vaccination has been effective in reducing the incidence of SSPE in both developing and industrialised countries,[1,2] and the risks of remaining unimmunised are considered to be greater than those arising from immunisation.

1. Anonymous. SSPE in the developing world. *Lancet* 1990; 336: 600.
2. Immunization Practices Advisory Committee. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR* 1996; 45 (RR 12): 1–35.

Effects on the skin. Stevens-Johnson syndrome was associated with measles vaccination in a 10-month-old infant.[1]

1. Hazir T, *et al.* Stevens-Johnson syndrome following measles vaccination. *J Pakistan Med Assoc* 1997; 47: 264–5.

High-titre vaccines and mortality. After reports of excess mortality in children, especially among girls, who received high-titre Edmonston-Zagreb (EZ) measles vaccine,[1] WHO reversed its recommendation for the use of this vaccine in its Expanded Programme on Immunization in developing countries.[2,3] Subsequent study[4] of children who had received high-titre EZ vaccine showed adverse effects on the nutritional status in either sex, confirming a generally deleterious effect of the vaccine. Others, however, have argued that the problems associated with the use of EZ vaccine have been exaggerated.[5,6] A review[6] pointed out that excess mortality was not seen in all studies, and concluded that the problem was unlikely to be due to the vaccine itself.

1. Knudsen KM, *et al.* Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996; 25: 665–73.
2. Anonymous. High-titre measles vaccines dropped. *Lancet* 1992; 340: 232.
3. WHO. Expanded Programme on Immunization: safety of high-titre measles vaccines. *Wkly Epidem Rec* 1992; 67: 357–61.
4. Garenne M. Effect of Edmonston-Zagreb high-titre vaccine on nutritional status. *Lancet* 1994; 344: 261–2.
5. Bennett JV, *et al.* Edmonston-Zagreb measles vaccine: a good vaccine with an image problem. *Pediatrics* 1999; 104: 1123–4.
6. Aaby P, *et al.* High-titer measles vaccination before 9 months of age and increased female mortality: do we have an explanation? *Semin Pediatr Infect Dis* 2003; 14: 220–32.

Precautions

As for vaccines in general, p. 2375.2.

Measles vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response, but they have been given to younger infants when the risk of measles is particularly high (see Immunisation Schedules, under Uses, p. 2398.3, for further discussion).

Hypersensitivity. For discussion of precautions to be taken on giving measles vaccines to children allergic to egg, see Measles, Mumps, and Rubella Vaccines, p. 2401.1.

Immunocompromised patients. For a discussion of the use of live vaccines in immunocompromised patients including those with HIV infection, see Precautions on p. 2375.2.

As with other live vaccines, measles vaccine is generally not recommended for use in patients with impaired immunity, although combined measles, mumps, and rubella vaccine may be given to HIV-positive individuals unless they have severe immunosuppression or other contra-indications. WHO[1,2] recommend that children with suspected or confirmed HIV infection or in areas where there is a high incidence of both HIV infection and measles should receive a dose of measles vaccine at 6 months of age in addition to the scheduled dose at 9 months. Immunocompromised patients who come into contact with measles should be given normal immunoglobulin. Specific measles immunoglobulins (p. 2398.2) have been used in some countries. Although measles vaccines have been given to immunocompromised patients without causing adverse effects[3] there have been some reports of severe reactions; disseminated measles infection was reported in a child with severe congenital immunodeficiency,[4] and fatal giant-cell pneumonitis was reported in an adult with AIDS.[5]

1. 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 12/02/10)
2. WHO. WHO recommendations for routine immunization–summary tables (issued 9 June 2010). Available at: http://www.who.int/immunization/policy/Immunization_tables/en/print.html (accessed 27/08/10)
3. Krasinski K, Borkowsky W. Measles and measles immunity in children infected with human immunodeficiency virus. *JAMA* 1989; 261: 2512–16.
4. Monafo WJ, *et al.* Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr* 1994; 124: 273–6.
5. Angel JB, *et al.* Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med* 1998; 129: 104–6.

Inflammatory bowel disease. Measles vaccination has been suggested as a possible factor in the development of inflammatory bowel disease.[1] However a case-control study involving 140 patients with inflammatory bowel disease provided no support for this hypothesis,[2] and measles virus has not been detected in biopsy specimens from patients with inflammatory bowel disease.[3] Later reviews[4-6] concluded that there is no evidence of any association between measles-containing vaccines and inflammatory bowel disease. A suggested link between measles vaccine-associated inflammatory bowel disease and autism is now refuted (see p. 2401.1).

1. Thompson NP, *et al.* Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995; 345: 1071–4.
2. Feeney M, *et al.* A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997; 350: 764–6.
3. Afzal MA, *et al.* Absence of measles-virus genome in inflammatory bowel disease. *Lancet* 1998; 351: 646–7.
4. Davis RL, Bohlke K. Measles vaccination and inflammatory bowel disease: controversy laid to rest? *Drug Safety* 2001; 24: 939–46.
5. Seagroatt V, Goldacre MJ. Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979-1998. *J Epidemiol Community Health* 2003; 57: 883–7.
6. Demicheli V, *et al.* Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06).

Interactions

As for vaccines in general, p. 2375.3

Vitamin A. Supplementation with vitamin A (see Deficiency States, p. 2099.2) is now included as part of WHO's Expanded Programme on Immunization.[1] There has been conflicting evidence of the effects of such supplementation on the response to measles vaccination. One study[2] reported a reduced immune response if vaccination occurs at 6 months (before the age at which measles vaccination is usually given in the EPI) while others[3,4] generally found no significant change in seroconversion or immune response in children vaccinated at 9 months (the age at which vaccination is generally started).

1. 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 12/02/10)
2. Semba RD, *et al.* Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 1995; 345: 1330–2.
3. Benn CS, *et al.* Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, West Africa. *Lancet* 1997; 350: 101–5.
4. Cherian T, *et al.* Effect of Vitamin A supplementation on the immune response to measles vaccination. *Vaccine* 2003; 23: 2418–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Rimevax†; *Cz.*: Movivac†; *Fr.*: Rouvax; *Ger.*: Masern-Impfstoff Merieux; *Gr.*: Moraten; *India*: M-Vac; *Israel*: Rouvax†; *Mex.*: Rimevax†; *NZ*:

The symbol † denotes a preparation no longer actively marketed

Rimevax; *Philipp.*: Rouvax; *Pol.*: Rouvax; *S.Afr.*: Diplovax†; Morbilvax†; Rimevax†; Rouvax; *Singapore*: Moraten; *Spain*: Rimevax†; *Turk.*: Moraten; Rouvax; *USA*: Attenuvax†.

Pharmacopoeial Preparations
Ph. Eur.: Measles Vaccine (Live).

Measles and Mumps Vaccines

Vacuna del sarampión y las paperas; Vacunas del sarampión y la parotiditis.
ATC — J07BD51.

Uses and Administration

Measles and mumps vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (below) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, and Mumps Vaccines, p. 2402.3.

Effects on the bones and joints. For a reference to arthritis occurring after measles and mumps vaccine, see under Adverse Effects and Precautions of Measles, Mumps, and Rubella Vaccines, below.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles-containing vaccines, see under Measles, Mumps, and Rubella Vaccines, below.

Interactions

As for vaccines in general, p. 2375.3.
See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Si Lin (思林); *Cz.*: Mopavac†; *Gr.*: Rouvax.

Measles and Rubella Vaccines

Vacunas del sarampión; Vacunas del sarampión y la rubéola.
ATC — J07BD53.

Uses and Administration

Measles and rubella vaccines may be used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (below) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, and Rubella Vaccines, p. 2417.2.

Incidence of adverse effects. Eight million children aged between 5 and 16 years were immunised with a measles and rubella vaccine in 1994 in the UK. By October 1995 the UK CSM had received reports on 2735 suspected adverse reactions most of which were minor and self-limiting.[1] Serious suspected reactions were rare and generally the number of reported cases was consistent with the background frequency of the particular disorder.

1. CSM/MCA. Adverse reactions to measles rubella vaccine. *Current Problems* 1995; 21: 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20156336&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles-containing vaccines, see under Measles, Mumps, and Rubella Vaccines, below.

Effects on the nervous system. Optic neuritis was reported in 2 children given measles and rubella vaccine 2 to 3 weeks previously.[1]

1. Stevenson VL, *et al.* Optic neuritis following measles/rubella vaccination in two 13-year-old children. *Br J Ophthalmol* 1996; 80: 1110–11.

Interactions

As for vaccines in general, p. 2375.3.
See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: MoRu-Viraten†; *Chile*: MoRu-Viraten; *Mex.*: Moruviraten†.

Measles, Mumps, and Rubella Vaccines

MMR Vaccines; Vacunas del sarampión, de la rubéola y de la parotiditis epidémica; Vacunas del sarampión, de la rubéola y de las paperas; Vacunas del sarampión, la parotiditis y la rubéola; Vacunas triples víricas.
ATC — J07BD52.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles, Mumps and Rubella Vaccine (Live); Vaccinum Morbillorum, Parotitidis et Rubellae Vivum). A freeze-dried preparation containing suitable live attenuated strains of measles virus, mumps virus (*Paramyxovirus parotitidis*), and rubella virus. The vaccine is prepared immediately before use by reconstitution from the dried vaccine. It contains in each dose not less than 3.0 log $CCID_{50}$ of infective measles virus, not less than 3.7 log $CCID_{50}$ of infective mumps virus, and not less than 3.0 log $CCID_{50}$ of infective rubella virus. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that MMR may be used on the label.

Uses and Administration

Measles, mumps, and rubella vaccines are used for active immunisation against measles, mumps, and rubella. They are used for primary immunisation in children 12 months of age or older and to protect susceptible contacts during an outbreak of measles. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

In the UK, it is recommended that all children receive two doses of 0.5 mL of a measles, mumps, and rubella vaccine by intramuscular injection (or subcutaneously if there is a bleeding disorder). These are usually given shortly after the first birthday and before school entry, but may be given at any age if routine vaccination has been omitted, allowing 3 months between doses. The combined vaccine may also be used for prophylaxis after exposure to measles provided it is given within 72 hours of contact. However, it is not considered to be effective for postexposure prophylaxis against either mumps or rubella. If the vaccine is given before 12 months of age, re-immunisation will be necessary starting at between 12 and 15 months with a further dose according to national schedules.

Similar schedules are used in the USA.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.
See also under Measles Vaccines, p. 2399.1, Mumps Vaccines, p. 2402.3, and Rubella Vaccines, p. 2417.2.

Events due to the measles component usually occur 6 to 11 days after vaccination and those due to the mumps and rubella components after 2 to 3 weeks but may occur up to 6 weeks after vaccination.

Adverse effects tend to be less frequent after the second dose of vaccine than after the first dose.

Measles, mumps, and rubella vaccines should not be given to individuals with a confirmed anaphylactic reaction to any antibacterial such as neomycin or kanamycin, that may be used in the manufacturing process.

Recommendations on vaccination in persons with egg allergy are discussed under Hypersensitivity, p. 2401.1.

Incidence of adverse effects. A double-blind placebo-controlled crossover study[1] in 581 pairs of twins showed that the frequency of adverse effects from the use of measles, mumps and rubella (MMR) vaccine was between 0.5 and 4.0%, indicating that adverse reactions are much less common than was previously thought. A study in the USA[2] showed that children given the vaccine at age 4 to 6 years had fewer adverse effects than those given it at 10 to 12 years. A later study[3] based on family reported symptoms was unable to detect any vaccine-related adverse effects when the second dose of MMR vaccine was given at either 4 to 6 years or 10 to 12 years. Vaccine-related adverse effects after the first dose of MMR vaccine were reported in about 17% in those vaccinated between the age of 12 and 20 months.

A further study[4] that assessed the effect of almost 3 million doses of vaccines in 1.8 million individuals revealed that 173 potentially serious reactions were claimed to have been caused by vaccination. There were 77 neurologic, 73 allergic, and 22 miscellaneous reactions recorded, and 1 death reported. However, 45% of the reactions were probably caused by some other factor. It was therefore concluded that serious events caused by MMR vaccine are rare and are greatly outweighed by the risks of the natural diseases.

1. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine: a double-blind placebo-controlled trial in twins. *Lancet* 1986; i: 939–42.
2. Davis RL, *et al.* MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the vaccine safety datalink project. *Pediatrics* 1997; 100: 767–71.
3. LeBaron CW, *et al.* Evaluation of potentially common adverse events associated with the first and second doses of measles-mumps-rubella vaccine. *Pediatrics* 2006; 118: 1422–30.
4. Patja A, *et al.* Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J* 2000; 19: 1127–34.

Effects on the blood. Thrombocytopenia occurs rarely in children receiving measles, mumps, and rubella (MMR) vaccine and usually resolves spontaneously. The rubella component is considered to be the most likely cause. An increased incidence of thrombocytopenia after the second dose of the vaccine has been reported in children who developed thrombocytopenia after the first dose.[1] A study[2] by the UK Public Health Laboratory Service suggested a link between MMR vaccine and the occurrence of immune thrombocytopenia, with an absolute risk of 1 in 22 300 of occurrence within 6 weeks of the first dose of the vaccine, and 2 out of every 3 cases attributable to it. Children with immune thrombocytopenia before receiving MMR vaccine had no vaccine-associated recurrences. A further study[3] of children aged 13 to 24 months and diagnosed with immune thrombocytopenia for the first time between January 1988 and December 1999 similarly found the attributable risk of developing it within 6 weeks of receiving the vaccine to be about 1 in 25 000. As a consequence of these findings, the UK CSM has recommended[4] that children developing immune thrombocytopenia within 6 weeks of vaccination with MMR vaccine, or any of its components, should have serological testing before their second dose is due; if this suggests that full immunity is not established, then a second dose should be given. A retrospective analysis of the CDC's Vaccine Safety Datalink between 1991 and 2000 also reported a strong association between MMR vaccination and the risk of immune thrombocytopenia in children 12 to 23 months of age. The association was strongest among those 12 to 15 months of age and was higher for boys than girls; the attributable risk of developing immune thrombocytopenia was 1 in 40 000 doses.[5]

1. Vlacha V, *et al.* Recurrent thrombocytopenic purpura after repeated measles-mumps-rubella vaccination. *Pediatrics* 1996; 97: 738–9.
2. Miller E, *et al.* Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001; 84: 227–9.
3. Black C, *et al.* MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol* 2003; 55: 107–11.
4. CSM/MCA. MMR vaccine and idiopathic thrombocytopenic purpura. *Current Problems* 2001; 27: 15. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 24/05/06)
5. France EK, *et al.* Vaccine Safety Datalink Team. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics* 2008; 121: e687–92.

Effects on the bones and joints. Arthralgia and arthritis occurring in patients given mumps, measles, and rubella vaccines have generally been attributed to the rubella component.[1] However, arthritis has been reported in an infant after vaccination with measles and mumps vaccine.[2]

1. Benjamin CM, *et al.* Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. *BMJ* 1992; 304: 1075–8.
2. Nussinovitch M, *et al.* Arthritis after mumps and measles vaccination. *Arch Dis Child* 1995; 72: 348–9.

Effects on hearing. Hearing loss is a known complication of wild measles and mumps viral infections, and the live attenuated strains of these viruses used in the vaccines might therefore have the potential to affect hearing. There have been individual case reports of sensorineural hearing loss after measles vaccination.[1,2] Profound, irreversible sensorineural deafness was reported in a 27-year-old woman after administration of a measles and rubella vaccine.[3] Nine cases of sensorineural hearing loss after measles, mumps, and rubella (MMR) vaccine were reported to the UK CSM between 1988 and 1993.[4] Of these, 3 cases were judged not to have been associated with the vaccine. In the remaining 6, the mumps virus component was considered to be the most likely cause of deafness if the vaccine was to blame, but the risk was considered to be small compared with the risks of natural infection. In the USA, a review of reports to the Vaccine Adverse Events Reporting System (VAERS) between 1990 and 2003 identified 44 cases of sensorineural hearing loss after doses of live attenuated measles and/or mumps vaccines; an additional 11 cases were identified from published reports. The onset of hearing loss in most cases was in keeping with the incubation periods of wild measles and mumps viruses. Based on the annual usage of MMR

vaccine, an estimated rate of hearing loss was reported to be 1 in 6 to 8 million doses.[5]

1. Watson JG. Bilateral hearing loss in a 3-year-old girl following measles immunisation at the age of 15 months. *Int J Pediatr Otorhinolaryngol* 1990; 19: 189–90.
2. Jayarajan V, Sedler PA. Hearing loss following measles vaccination. *J Infect* 1995; 30: 184–5.
3. Hulbert TV, *et al.* Bilateral hearing loss after measles and rubella vaccination in an adult. *N Engl J Med* 1991; 325: 134.
4. Stewart BJA, Prabhu PU. Reports of sensorineural deafness after measles, mumps, and rubella immunisation. *Arch Dis Child* 1993; 69: 153–4.
5. Asatryan A, *et al.* Live attenuated measles and mumps viral strain-containing vaccines and hearing loss: Vaccine Adverse Event Reporting System (VAERS), United States, 1990—2003. *Vaccine* 2008; 26: 1166–72.

Effects on the nervous system. Although there have been case reports[1] linking Guillain-Barré syndrome with measles, mumps, and rubella vaccine, a retrospective study[2] that involved 189 patients with the syndrome and about 630 000 recipients of the vaccine could not find a causal association.

Prolonged tonic-clonic seizures were associated with prolonged hemiparesis in a 16-month-old girl 6 days after measles, mumps, and rubella vaccination.[3] There was evidence of transient encephalopathy. However, a causal relationship between measles-containing vaccines and encephalitis is generally considered to be unlikely. Other reported neurological effects after vaccination include gait disturbances,[4,5] and transverse myelitis.[6] However, a retrospective study[7] found no evidence for a causal association between vaccination and acute ataxia and the development of gait disturbances and suggested the original reports represented chance occurrence.

For discussion of meningitis and encephalitis occurring after measles, mumps, and rubella vaccination, see under Adverse Effects of Mumps Vaccines, p. 2402.3.

1. Morris K, Rylance G. Guillain-Barré syndrome after measles, mumps, and rubella vaccine. *Lancet* 1994; 343: 60.
2. Patja A, *et al.* Risk of Guillain-Barré syndrome after measles-mumps-rubella vaccination. *J Pediatr* 2001; 138: 250–4.
3. Sackey AH, Broadhead RL. Hemiplegia after measles, mumps, and rubella vaccination. *BMJ* 1993; 306: 1169.
4. Plesner A-M. Gait disturbances after measles, mumps, and rubella vaccine. *Lancet* 1995; 345: 316.
5. Plesner AM, *et al.* Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study. *Acta Paediatr* 2000; 89: 58–63.
6. Joyce KA, Rees JE. Transverse myelitis after measles, mumps, and rubella vaccine. *BMJ* 1995; 311: 422.
7. Miller E, *et al.* No evidence of an association between MMR vaccine and gait disturbance. *Arch Dis Child* 2005; 90: 292–6.

Hypersensitivity. Since the measles and mumps components of measles, mumps, and rubella vaccines are grown in cell cultures of chick embryos the vaccine was formerly contra-indicated in individuals with a history of anaphylactic reactions to egg. In both the UK and USA, serious reactions to egg including anaphylaxis are no longer regarded as absolute contra-indications to vaccination although specialist advice should be obtained and vaccination performed only under controlled conditions. It is generally agreed that the vaccine can be given safely to children with less severe reactions to eggs.

A confirmed anaphylactic reaction to gelatin, kanamycin, or neomycin is a contra-indication to measles, mumps, and rubella vaccines.

Inflammatory bowel disease and autism. A controversial report[1] in 1998 linked measles, mumps, and rubella vaccination with the development of inflammatory bowel disease and behavioural abnormalities including autism. However, there is now overwhelming evidence from studies and analyses that the vaccine does not cause autism.[2-12] Similarly, the link between measles-containing vaccines and inflammatory bowel disease has not been substantiated (see under Precautions for Measles Vaccines, p. 2399.3).

1. Wakefield AJ, *et al.* Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2. Peltola H, *et al.* No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet* 1998; 351: 1327–8.
3. Roberts R. There is no causal link between MMR vaccine and autism. *BMJ* 1998; 316: 1824.
4. Taylor B, *et al.* Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999; 353: 2026–9.
5. Kaye JA, *et al.* Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001; 322: 460–3. Correction. *ibid.*; 720.
6. Dales L, *et al.* Time trends in autism and in MMR immunization coverage in California. *JAMA* 2001; 285: 1183–5.
7. Halsey NA, *et al.* Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the new challenges in childhood immunizations conference convened in Oak Brook, Illinois, June 12-13, 2000. Abstract: *Pediatrics* 2001; 107: 1174. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/5/e84 (accessed 14/12/04)
8. Smeeth L, *et al.* MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 2004; 364: 963–9.
9. Immunization Safety Review Committee. *Immunization safety review: vaccines and autism.* Washington, DC: National Academy Press, 2004. Available at: http://www.nap.edu/catalog.php?record_id=10822 (accessed 26/08/10)
10. Demicheli V, *et al.* Vaccines for measles, mumps and rubella in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/05/06)
11. 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&ch-k=isTIGX (accessed 27/08/10)
12. Hornig M, *et al.* Lack of association between measles virus vaccine and autism with enteropathy: a case-control study. *PLoS One* 2008; 3: e3140.

Orchitis. Orchitis is a common complication of wild-type mumps infection, particularly in post-pubertal males, and a few cases of bilateral and unilateral orchitis following vaccination with measles, mumps, and rubella vaccine have been reported.[1,2] An 18-year-old adolescent developed swelling 11 days after vaccination[1]; he was treated with NSAIDs and the swelling resolved.[1] A 12-month-old child developed scrotal and testicular swelling 2 weeks after vaccination which resolved spontaneously over several days, while 2 post-pubertal patients (36 and 37 years of age) developed swelling 3 days after vaccination; in both patients the swelling also spontaneously resolved within 1 to 5 weeks.[2]

1. Abdelbaky AM, *et al.* Unilateral epididymo-orchitis: a rare complication of MMR vaccine. *Ann R Coll Surg Engl* 2008; 90: 336–7.
2. Clifford V, *et al.* Mumps vaccine associated orchitis: evidence supporting a potential immune-mediated mechanism. *Vaccine* 2010; 28: 2671–3.

Interactions

As for vaccines in general, p. 2375.3.

See also under Measles Vaccines, p. 2399.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: MMR II; Trimovax; Triviraten; *Austral.*: Priorix; *Austria*: MMRVaxPro; Priorix; *Belg.*: MMRVaxPro; Priorix; *Braz.*: Vacina Comb. Contra Sarampo, Caxumba e Rubeola; Vacina Contra Sarampo, Caxumba e Rubeola; Vacina de Virus Vivos de Sarampo, Caxumba e Rubeola; *Canad.*: MMR II; Priorix; *China*: MMR II (默尔康); Priorix (普祥立适); *Cz.*: MMR II†; MMRVaxPro; Priorix; Trivivac; *Denm.*: MMR†; Priorix; *Fin.*: MMR II†; Priorix; *Fr.*: MMRVaxPro; Priorix; R.O.R.†; *Ger.*: MMR Triplovax†; MMRVaxPro; Priorix; *Gr.*: MMR II; MMRVaxPro; Pluserix; Priorix; *Hong Kong*: MMR II; Priorix; Trimovax; *Hung.*: MMR II†; Priorix; *India*: Morupar; Tresivac; *Indon.*: MMR II; Trimovax; *Irl.*: MMR II†; MMRVaxPro; Priorix; *Israel*: MMR II; Priorix; *Ital.*: MMR II†; MMRVaxPro; Priorix; *Malaysia*: MMR II; Priorix; *Mex.*: MMR II; Priorix; *Neth.*: MMRVaxPro; Priorix; *Norw.*: MMR II†; MMRVaxPro; Priorix; *NZ*: MMR II; Priorix; Triviraten†; *Philipp.*: Priorix; Trimovax; Triviraten†; *Pol.*: MMR II†; MMRVaxPro; Priorix; *Port.*: MMR II†; MMRVaxPro; Priorix; *Rus.*: MMR II (ММР II); Priorix (Приорикс); *S.Afr.*: Priorix; Trimovax; *Singapore*: MMR II; Priorix; *Spain*: MMRVaxPro; Priorix; Vacuna Triple MSD†; *Swed.*: MMR II†; MMRVaxPro; Priorix; *Switz.*: MMRVaxPro; Priorix; *Thai.*: MMR II; Priorix; Trimovax; *Turk.*: MMR II; Priorix; Trimovax; Triviraten; *UK*: MMR II†; MMRVaxPro; Priorix; *USA*: MMR II; *Venez.*: Priorix.

Pharmacopoeial Preparations

Ph. Eur.: Measles, Mumps, and Rubella Vaccine (Live).

Measles, Mumps, Rubella, and Varicella-Zoster Vaccines

MMRV Vaccines.

ATC — J07BD54.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Measles, Mumps, Rubella and Varicella Vaccine (Live); Vaccinum Morbillorum, Parotitidis, Rubellae et Varicellae Vivum). A freeze-dried preparation containing suitable live attenuated strains of measles virus, mumps virus (*Paramyxovirus parotitidis*), rubella virus, and human herpesvirus 3. The vaccine is prepared immediately before use by reconstitution from the dried vaccine. It contains in each dose not less than 3.0 log $CCID_{50}$ of infective measles virus, not less than 3.7 log $CCID_{50}$ of infective mumps virus, and not less than 3.0 log $CCID_{50}$ of infective rubella virus. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

Profile

Measles, mumps, rubella, and varicella-zoster vaccines are used for active immunisation against measles, mumps, rubella and varicella (chickenpox).

In the USA, the Advisory Committee on Immunization Practices (ACIP) states that the measles, mumps, rubella, and varicella (MMRV) vaccine may be given to children aged 12 months to 12 years for simultaneous vaccination against these viral diseases. Surveillance data indicate an increased risk of febrile seizure in children after their first dose of MMRV vaccine, compared with those who were given separate injections of measles, mumps, and rubella (MMR) vaccine and varicella vaccine at the same visit. The ACIP therefore no longer expresses a preference for use of the quadrivalent vaccine over separate injections of equivalent component vaccines.

Reviews.

1. Vesikari T, *et al.* Increasing coverage and efficiency of measles, mumps, and rubella vaccine and introducing universal varicella vaccination in Europe: a role for the combined vaccine. *Pediatr Infect Dis J* 2007; 26: 632–8.
2. Ramet J. A new challenge for Europe: introducing a pediatric quadrivalent vaccine for measles, mumps, rubella, and varicella. *Int J Infect Dis* 2007; 11 (suppl 2): S49–S55.
3. Dhillon S, Curran MP. Live attenuated measles, mumps, rubella, and varicella zoster virus vaccine (Priorix-Tetra). *Paediatr Drugs* 2008; 10: 337–47.
4. Czajka H, *et al.* A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. *Vaccine* 2009; 27: 6504–11.
5. CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59 (RR-3): 1–12. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5903.pdf (accessed 25/06/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Priorix-Tetra; *Canad.*: Priorix-Tetra; *Cz.*: Priorix-Tetra; ProQuad; *Denm.*: Priorix-Tetra; *Fin.*: Priorix-Tetra†; *Ger.*: Priorix-Tetra; *Gr.*: Priorix-Tetra; *Irl.*: Priorix-Tetra; ProQuad; *Israel*: Priorix-Tetra; *Ital.*: Priorix-Tetra; ProQuad; *Malaysia*: Priorix-Tetra; *Neth.*: Priorix-Tetra; ProQuad; *NZ*: Priorix-Tetra; ProQuad; *Pol.*: ProQuad; *Port.*: Priorix-Tetra; ProQuad; *Singapore*: Priorix-Tetra; *Switz.*: Priorix-Tetra; *Thai.*: Priorix-Tetra; *USA*: ProQuad.

Pharmacopoeial Preparations

Ph. Eur.: Measles, Mumps, Rubella and Varicella Vaccine (Live).

Meningococcal Vaccines

Vacunas de polisacáridos meningocócicos.

ATC — J07AH01; J07AH02; J07AH03; J07AH04; J07AH05; J07AH06; J07AH07; J07AH08; J07AH09; J07AH10.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Meningococcal Polysaccharide Vaccine; Vaccinum Meningitidis Cerebrospinalis). It consists of one or more purified capsular polysaccharides obtained from one or more suitable strains of *Neisseria meningitidis* group A, group C, group Y, and group W135; it may contain a single type of polysaccharide or any mixture of the types. It is prepared immediately before use by reconstitution from the stabilised freeze-dried vaccine with a suitable sterile liquid. The freeze-dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Men plus the relevant antigen may be used on the label (for example MenAC).

Ph. Eur. 8: (Meningococcal Group C Conjugate Vaccine; Vaccinum Meningococcale Classis C Coniugatum). A liquid or freeze-dried preparation of purified capsular polysaccharide derived from a suitable strain of *Neisseria meningitidis* group C covalently linked to a carrier protein. The vaccine may contain an adjuvant. The freeze-dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that MenC(conj) may be used on the label.

Uses and Administration

Meningococcal vaccines are used for active immunisation against *Neisseria meningitidis* infections, which include meningitis and septicaemia (see Meningococcal Infections, p. 192.1). They are preparations of purified polysaccharide antigens from *N. meningitidis* and may be monovalent, containing the antigen of only one serotype of *N. meningitidis* or polyvalent, containing antigens of two or more serotypes. Conjugation of the polysaccharide to a carrier such as diphtheria CRM_{197} protein or to tetanus toxoid protein increases the immunogenicity. While effective vaccines against some of the common serotypes of bacterial meningitis such as A, C, W135, and Y have been available and included in many national immunisation programmes, it has been more difficult to develop vaccines against the group B serotype. However, several avenues of research have now resulted in the production of an effective vaccine against this serotype.

In the UK, primary immunisation is recommended during childhood with a further dose given during adolescence, whereas in the USA routine immunisation is recommended during adolescence or for those at increased risk for meningococcal disease from 6 weeks of age. In the UK, a conjugate meningococcal C vaccine is used and is generally given by intramuscular injection with the subcutaneous route reserved for patients with haemophilia or thrombocytopenia. The primary immunisation course for infants consists of a single dose of 0.5 mL given at 3 months of age. The first booster dose with a combined conjugate

meningococcal C and *Haemophilus influenza* type b vaccine is recommended at 12 to 13 months of age with a further booster dose of conjugate meningococcal C vaccine given around 14 years of age. In the USA, routine immunisation with a single dose of a conjugate tetravalent vaccine from groups A, C, Y, and W135 is performed at 11 to 12 years of age, with a booster dose at 16 years of age. Catch up vaccinations may be given, however, routine vaccination of those aged 19 to 21 years who are not at increased risk for meningococcal disease is not recommended. For discussion of immunisation schedules see under Vaccines, p. 2373.3.

Asplenic persons or those who have terminal complement component deficiencies are at higher than normal risk of acquiring meningococcal infection and therefore they should be immunised. Either a conjugate meningococcal C vaccine or a tetravalent vaccine (A, C, Y, and W135, unconjugated or conjugated) may be used depending on availability and local immunisation guidelines.

Meningococcal vaccines are also indicated in persons travelling to countries where the risk of infection is high. They should receive a tetravalent meningococcal polysaccharide vaccine (either unconjugated or conjugated) rather than the group C conjugate vaccine, and should be immunised even if they have already received the latter. Vaccination is indicated particularly for visits of 1 month or more and for those backpacking or living or working with local residents. Vaccination is a visa requirement for pilgrims to Saudi Arabia.

Meningococcal vaccines may be given as an adjunct to chemoprophylaxis in contacts of persons with meningitis (see p. 191.1).

Strain-specific **meningitis B** vaccines based on bacterial outer membrane vesicles or proteins such as PorA, PorB, or NspA have successfully been used against epidemics in Norway, Cuba, and New Zealand. In 2013, an adsorbed meningococcal B vaccine containing 3 recombinant *N. meningitidis* group B proteins (NHBA fusion protein, NadA protein, and the fHbp fusion protein), and the outer membrane vesicles from *N. meningitidis* group B strain NZ 98/254 was approved for use in Europe. It is given by intramuscular injection in usual doses of 0.5 mL; primary immunisation consists of three doses given at intervals of one month, starting preferably at 2 months of age. A single reinforcing dose is recommended between 12 and 23 months of age.

Guidelines and recommendations.

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2. CDC. Updated recommendations for use of meningococcal conjugate vaccines—Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2011; **60**: 72–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a3.htm (accessed 14/03/13)
3. American Academy of Pediatrics. Committee on Infectious Diseases. Meningococcal conjugate vaccines policy update: booster dose recommendations. *Pediatrics* 2011; **128**: 1213–8. Also available at: http://pediatrics.aappublications.org/content/128/6/1213.full.pdf+html (accessed 04/04/13)
4. WHO. Meningococcal vaccines: WHO position paper, November 2011. *Wkly Epidem Rec* 2011; **86**: 521–39. Also available at: http://www.who.int/wer/2011/wer8647.pdf (accessed 08/03/13)
5. CDC. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013; **62** (RR-2): 1–28. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf (accessed 04/04/13)
6. CDC. Infant meningococcal vaccination: Advisory Committee on Immunization Practices (ACIP) recommendations and rationale. *MMWR* 2013; **62**: 52–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm (accessed 08/03/13)

Reviews and references.

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5. Smith MJ. Meningococcal tetravalent conjugate vaccine. *Expert Opin Biol Ther* 2008; **8**: 1941–6.
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8. Lewis S, *et al.* Challenges and progress in the development of a serogroup B meningococcal vaccine. *Expert Rev Vaccines* 2009; **8**: 729–45.
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10. Poland GA. Prevention of meningococcal disease: current use of polysaccharide and conjugate vaccines. *Clin Infect Dis* 2010; **50** (suppl 2): S45–S53.
11. Tan LK, *et al.* Advances in the development of vaccines against Neisseria meningitidis. *N Engl J Med* 2010; **362**: 1511–20.
12. WHO: Initiative for Vaccine Research (IVR). Meningococcal disease. Information available at: http://www.who.int/vaccine_research/diseases/soa_bacterial/en/index1.html (accessed 08/04/13)
13. Findlow J, *et al.* Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin Infect Dis* 2010; **51**: 1127–37.
14. Gossger N, *et al.* Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; **307**: 573–82.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Immunity to the unconjugated serogroup C polysaccharide in meningococcal vaccines may be insufficient to confer adequate protection against infection in infants under about 2 years of age.

Effects on the nervous system. From June 2005 to September 2006, 17 cases of Guillain-Barré syndrome were reported to the Vaccine Adverse Event Reporting System (VAERS) after use of a tetravalent (A, C, W135, and Y) meningococcal conjugate vaccine (Menactra). Whether the cases were caused by the vaccine or were coincidental was unknown.[1,2] The CDC recommends that persons with a history of Guillain-Barré syndrome should not be vaccinated with the tetravalent meningococcal conjugate vaccine.[2]

1. CDC. Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine - United States, June-July 2005. *MMWR* 2005; **54**: 1023–5.
2. CDC. Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine— United States, June 2005-September 2006. *MMWR* 2006; **55**: 1120–4. Correction. *ibid.*: 1177.

Pregnancy and the neonate. A study[1] in 157 Asian women given a tetravalent polysaccharide vaccine in the third trimester of pregnancy found that immunisation was safe for both mothers and infants. Infants were provided with significantly increased levels of IgG for 2 to 3 months and of oral IgA for 6 months from breast feeding.

1. Shahid NS, *et al.* Placental and breast transfer of antibodies after maternal immunization with polysaccharide meningococcal vaccine: a randomized, controlled evaluation. *Vaccine* 2002; **20**: 2404–9.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antimeningococica A+C; Menjugate; Menomune; Menveo; NeisVac-C; Va-Mengoc-BC; *Austral.*: Mencevax ACWY; Meningitec; Menjugate; Menomune; Menveo; NeisVac-C; *Austria*: Mencevax ACWY; Meningitec†; Menjugate; Menveo; NeisVac-C; *Belg.*: Mencevax ACWY; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; *Braz.*: Vacina Meningococica A+C; Vacina Meningococica Conjugada Grupo C; Vacina Meningococica Conjugada Grupo C; *Canad.*: Menactra; Meningitec; Menjugate; Menomune; Menveo; NeisVac-C; *Chile*: Meningo A+C†; NeisVac-C; *China*: Meng Ling Kang (梦灵康); MeningACon (盟纳康); Meningo A +C (美宁安 A+C); Menwayc (盟威克); Nao Man Ning (瑞帷宁); Yu Nao Ning (御脑宁); Yu Nao Ning A+C (御脑宁A+C); *Cz.*: Menjugate; Menveo; NeisVac-C; *Denm.*: Meningitec; Meningovax A+C†; Menjugate; Menveo; NeisVac-C; Nimenrix; *Fin.*: Mencevax ACWY; Meningovax A+C†; Menjugate†; NeisVac-C; *Fr.*: Mencevax; Meningitec; Meninvact†; Menjugate; Menomune†; Menveo; NeisVac; *Ger.*: Mencevax ACWY; Meningitec; Meningokokken-Impfstoff A + C; Menjugate; Menveo; NeisVac-C; *Gr.*: Meningitec; Meninvact; Menjugate; Menomune; Menveo; NeisVac-C; Vaccin Meningococcique; *Hong Kong*: Mencevax ACWY; *Hung.*: Mencevax ACWY; Meningitec; Meningo A+C; Menjugate; NeisVac-C; *India*: Mencevax; *Indon.*: Mencevax ACWY; *Irl.*: Meningitec; Menjugate; Menveo; NeisVac-C; *Israel*: Mencevax ACWY; Menveo; *Ital.*: Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; *Malaysia*: Mencevax ACWY; Menomune; *Mex.*: Va-Mengoc-BC; *Neth.*: Meningitec; Meningovax A+C†; Meninvact†; Menjugate; Menveo; NeisVac-C; Nimenrix; *Norw.*: Meningitec†; Meningovax A +C†; Menveo; NeisVac-C; Nimenrix; *NZ*: Mencevax ACWY; Meningitec; Menomune; MeNZB†; NeisVac-C; *Philipp.*: Euro A & C; Menactra; Mencevax ACWY; Menomune; Menovac; *Pol.*: Meningitec; Menveo; NeisVac-C; *Port.*: Meningitec; Menjugate; Menveo; NeisVac-C; *Rus.*: Mencevax ACWY (Менцевакс ACWY); *S.Afr.*: Imovax Meningo A & C†; Mencevax; *Singapore*: Menactra; Mencevax ACWY; Menomune†; *Spain*: Mencevax AC†; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; *Swed.*: Meningovax A+C†; Menveo; NeisVac-C; *Switz.*: Mencevax ACWY; Meningitec; Menjugate; NeisVac-C; *Thai.*: Menomune; *Turk.*: Imovax Meningo A+C†; *UK*: ACWY Vax; Bexsero; Meningitec; Menjugate; Menveo; NeisVac-C; Nimenrix; *USA*: Menactra; Menomune; Menveo.

Pharmacopoeial Preparations

Ph. Eur.: Meningococcal Group C Conjugate Vaccine; Meningococcal Polysaccharide Vaccine.

Multiple Sclerosis Vaccines

Vacunas de la esclerosis múltiple.

Profile

Vaccines based on T cells have been investigated for the management of multiple sclerosis.

The use of vaccine-derived polyclonal antibodies from the serum of goats is also under investigation.

References.

1. Hellings N, *et al.* T-cell vaccination in multiple sclerosis: update on clinical application and mode of action. *Autoimmun Rev* 2004; **3**: 267–75
2. Sospedra M, Martin R. Antigen-specific therapies in multiple sclerosis. *Int Rev Immunol* 2005; **24**: 393–413.
3. Fontoura P, *et al.* Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. *Int Rev Immunol* 2005; **24**: 415–46.
4. Correale J, *et al.* Vaccines for multiple sclerosis: progress to date. *CNS Drugs* 2008; **22**: 175–98.

Mumps Immunoglobulins

Inmunoglobulinas contra la parotiditis; Inmunoglobulinas contra las paperas.

ATC — J06BB15.

Profile

Preparations containing antibodies against mumps virus have been used in some countries for passive immunisation against mumps.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Paruman.

Mumps Vaccines

Vacunas de la parotiditis; Vacunas de las paperas.

ATC — J07BE01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Mumps Vaccine (Live); Vaccinum Parotitidis Vivum). A freeze-dried preparation containing a suitable live attenuated strain of mumps virus (*Paramyxovirus parotitidis*) grown in cultures of human diploid cells or chick-embryo cells or the amniotic cavity of chick embryos. It is prepared immediately before use by reconstitution from the dried vaccine. The cell-culture medium may contain the lowest effective concentration of a suitable antibacterial. The virus concentration is not less than 3.7 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Mumps may be used on the label.

Uses and Administration

Mumps vaccines are used for active immunisation against mumps.

For primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Many different attenuated strains of mumps virus have been used in vaccines and those commonly used have included Jeryl Lynn, Urabe, Leningrad-3 (and adapted L-Zagreb), and Rubini strains. Efficacy seems to be broadly similar for these strains with the exception of Rubini which is reported to be less effective than Jeryl Lynn or Urabe.

In some countries, a single-antigen mumps vaccine has been used although combined vaccines are usually preferred.

References.

1. WHO. Mumps virus vaccines: WHO position paper. *Wkly Epidem Rec* 2007; **82**: 51–60. Also available at: http://www.who.int/immunization/wer8207mumps_Feb07_position_paper.pdf (accessed 25/06/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Parotid swelling may occur. Unilateral nerve deafness, aseptic meningitis, and encephalitis have occurred rarely (see below for further discussion).

Mumps vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Effects on hearing. For reports of sensorineural hearing loss after vaccination with measles, mumps, and rubella-containing vaccines, see p. 2400.3.

Effects on the nervous system. There have been a few reports of neurological reactions including meningitis and encephalitis after vaccination with measles, mumps, and rubella (MMR) vaccines. These reactions have been attributed to the mumps component. However, it has not been possible to isolate the virus from the CSF in every case and identify it as either the vaccine strain or a wild-type strain. Meningitis develops up to 35 days after immunisation, is mild, and sequelae are rare.[1,2] One study[3] found the incidence of virus-positive post-immunisation meningitis from the Urabe strain of mumps vaccine to be about 1 in 11 000 immunised children, with the incidence following Jeryl Lynn mumps vaccine being much lower. This

result was supported by the incidence of about 1 in 4000 in another study,[4] making it less likely that this was a chance result, and much higher than the estimates of up to 1 in 1 million reported previously.[5] Subsequent research[6] identified the Urabe vaccine strain in CSF samples from all of 20 children with post-vaccination meningitis in the UK, and no isolates of the Jeryl Lynn strain in patients with meningitis among 80 samples tested. Thus, vaccines containing the Urabe strain, including combined MMR vaccines are no longer used in the UK and some other countries.[7] A relatively high incidence of meningitis of about 1 in 1000 has also occurred after use of a measles and mumps vaccine prepared from the Leningrad-3 strain of mumps virus.[8,9]

Encephalitis has been associated with mumps vaccination less frequently than meningitis, but may be more serious.[1] The Advisory Committee on Immunization Practices in the USA has reported that the incidence of encephalitis within 30 days of receiving a mumps-containing vaccine is 0.4 per one million doses.[10] This is no higher than the background incidence for CNS dysfunction seen in the general population. There are also a few reports of acute disseminated encephalomyelitis following vaccination with mumps vaccine.[11]

In considering the above data it should be remembered that mumps is the most common cause of meningoencephalitis in children under 15 years of age in the UK and an important cause of permanent sensorineural deafness in childhood.[1] Meningitis after natural mumps infection is estimated to occur in 1 in 400 cases, an incidence that is very considerably above any reported with vaccination.

1. Anonymous. Mumps meningitis and MMR vaccination. *Lancet* 1989; ii: 1015–16.
2. Maguire HC, *et al.* Meningoencephalitis associated with MMR vaccine. *Commun Dis Rep* 1991; 1 (review 6): R60–R61.
3. Miller E, *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* 1993; 341: 979–82.
4. Colville A, Pugh S. Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet* 1992; 340: 786. Correction. *Ibid.*: 986.
5. McDonald JC, *et al.* Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. *Pediatr Infect Dis J* 1989; 8: 751–5.
6. Forsey T, *et al.* Mumps vaccine and meningitis. *Lancet* 1992; 340: 980.
7. Anonymous. Two MMR vaccines withdrawn. *Lancet* 1992; 340: 722.
8. Čizman M, *et al.* Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J* 1989; 8: 302–8.
9. Tešović G, *et al.* Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet* 1993; 341: 1541.
10. Immunization Practices Advisory Committee. Mumps prevention. *MMWR* 1989; 38: 388–400.
11. Japanese Pharmaceuticals and Medical Devices Safety Information. Important safety information—freeze-dried live attenuated mumps vaccine; no. 279 (issued May 2011). Available at: www.pmda.go.jp/english/service/pdf/precautions/PMDSI-279.pdf (accessed 03/04/12)

Orchitis. For mention of orchitis following vaccination with measles, mumps, and rubella vaccine see under Measles, Mumps, and Rubella Vaccine, p. 2401.2.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Pavivac; *Gr.*: Mumpsvax; *Turk.*: Mumaten; *USA*: Mumpsvax†.

Pharmacopoeial Preparations
Ph. Eur.: Mumps Vaccine (Live).

Mycobacterium Vaccae Vaccines

SRL-172; Vacunas de Mycobacterium vaccae.

Profile

Vaccines containing *Mycobacterium vaccae* are under investigation for the prevention and immunotherapy of tuberculosis and other mycobacterial infections. They are also being studied for therapeutic use in asthma, eczema, psoriasis, and some malignant neoplasms.

Asthma. Heat-killed *Mycobacterium vaccae* is a potent down-regulator of T-helper 2 cytokines which play a central role in asthma. In a double-blind, randomised, placebo-controlled study[1] in 24 asthmatic men, a bronchial allergen challenge was given 2 weeks before and 3 weeks after a single intradermal injection of *Mycobacterium vaccae* vaccine. The maximum fall in FEV, during the allergic response to the latter challenge was reduced by a mean of 34%, but this was not statistically significant compared with placebo.

1. Camporota L, *et al.* The effects of Mycobacterium vaccae on allergen-induced airway responses in atopic asthma. *Eur Respir J* 2003; 21: 287–93.

Eczema. In a double-blind, randomised, placebo-controlled study[1] in 41 children aged 5 to 18 years with moderate to severe atopic dermatitis, an intradermal injection of *Mycobacterium vaccae* vaccine resulted in a 48% reduction in the surface area of the skin affected after 3 months compared with 4% in those given placebo. In a later study[2] in 56 children aged 2 to 6 years, these results could not be replicated because the reduction in affected area was not found to be significantly different from placebo.

1. Arkwright PD, David TJ. Intradermal administration of a killed Mycobacterium vaccae suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; 107: 531–4.
2. Arkwright PD, David TJ. Effect of Mycobacterium vaccae on atopic dermatitis in children of different ages. *Br J Dermatol* 2003; 149: 1029–34.

Malignant neoplasms. *Mycobacterium vaccae* vaccines have been used with limited success as adjunctive therapy in the management of a variety of cancers, notably prostate cancer, malignant melanoma, and non-small-cell lung cancer. In a preliminary study[1] 28 patients with inoperable non-small-cell lung cancer and mesothelioma were randomised to receive chemotherapy either with or without adjunctive intradermal injection of a heat-killed *Mycobacterium vaccae* vaccine (SRL-172). A trend towards improved response rate was found in those patients receiving combined therapy, together with improved median survival and 1-year survival rates; some patients given combined therapy were subsequently able to receive curative surgery or radical radiotherapy. A similar subsequent phase III study[2] in 419 patients found a significant improvement in patient quality of life after combined therapy, but the improvements in survival-time could not be replicated. Secondary analyses of these results[3] suggested an improvement in survival-time for patients with adenocarcinoma, but not for those with squamous cell carcinoma. There is also some evidence of beneficial effect in patients with metastatic renal cell carcinoma.[4]

1. O'Brien ME, *et al.* A randomized phase II study of SRL172 (Mycobacterium vaccae) combined with chemotherapy in patients with advanced inoperable non-small-cell lung cancer and mesothelioma. *Br J Cancer* 2000; 83: 853–7.
2. O'Brien ME, *et al.* SRL172 (killed Mycobacterium vaccae) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol* 2004; 15: 906–14.
3. Stanford JL, *et al.* Successful immunotherapy with Mycobacterium vaccae in the treatment of adenocarcinoma of the lung. *Eur J Cancer* 2008; 44: 224–7.
4. Patel PM, *et al.* An evaluation of a preparation of Mycobacterium vaccae (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer* 2008; 44: 216–23.

Psoriasis. Preliminary studies have shown that heat-killed *Mycobacterium vaccae* vaccines may induce periods of remission when given intradermally. An open-label study[1] in 24 patients given 2 intradermal injections into lesion-free deltoid skin at a 3-week interval found, 12 weeks after starting treatment: marked improvement (14 patients), moderate improvement (2), no change (6), and worsening of symptoms (2). By 24 weeks, 11 of 22 patients continued to show a greater than 50% improvement and of these 5 had complete clearance of skin lesions lasting for 6 months or more. In another study,[2] a more potent heat-killed, delipidated, deglycolipidated vaccine was given similarly to 20 patients with moderate to severe psoriasis; after 12 weeks, 13 of the 20 patients showed a marked improvement, 3 were unchanged, 3 had worsened, and 1 withdrawn due to an exfoliative flare. At 24 weeks, 13 of 19 patients continued to show a greater than 50% improvement, and in some this lasted for 6 months or more. A double-blind, randomised, placebo-controlled study[3] with the latter vaccine in 36 patients with psoriatic arthritis found no improvement in psoriatic lesions compared with placebo, although there did appear to be some improvement in pain experienced. Another placebo-controlled study in patients with psoriasis also failed to show benefit.[4]

1. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol* 2000; 39: 51–8.
2. Balagon MV, *et al.* Improvement in psoriasis after intradermal administration of delipidated, deglycolipidated Mycobacterium vaccae (PVAC): results of an open-label trial. *Clin Exp Dermatol* 2001; 26: 233–41.
3. Dalbeth N, *et al.* A randomised placebo controlled trial of delipidated, deglycolipidated Mycobacterium vaccae as immunotherapy for psoriatic arthritis. *Ann Rheum Dis* 2004; 63: 718–22.
4. Netto EM, *et al.* Phase II randomized, placebo-controlled trial of M. vaccae-derived protein (PVAC) for the treatment of psoriasis. *Vaccine* 2006; 24: 5056–63.

Tuberculosis. *IMMUNISATION.* References.

1. von Reyn CF, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of Mycobacterium vaccae vaccine. *Clin Infect Dis* 1998; 27: 1517–20.
2. Waddell RD, *et al.* Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clin Infect Dis* 2000; 30 (suppl 3): S309–S315.
3. Vuola JM, *et al.* Immunogenicity of an inactivated mycobacterial vaccine for the prevention of HIV-associated tuberculosis: a randomized, controlled trial. *AIDS* 2003; 17: 2351–5.
4. Yang XY, *et al.* Mycobacterium vaccae vaccine to prevent tuberculosis in high risk people: a meta-analysis. *J Infect* 2010; 60: 320–30.
5. Beresford B, Sadoff JC. Update on research and development pipeline: tuberculosis vaccines. *Clin Infect Dis* 2010; 50 (suppl 3): S178–S183.

IMMUNOTHERAPY. A systematic review[1] found that immunotherapy with *Mycobacterium vaccae* produced no beneficial effects in patients with tuberculosis.

1. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/12/04).

Normal Immunoglobulins

Immunoglobulinas inespecíficas.
ATC — J06BA01; J06BA02.
UNII — 66Y330CJHS (human immunoglobulin G).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Normal Immunoglobulin; Immunoglobulinum Humanum Normale). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG) antibodies, of normal subjects. Other proteins may be present; it contains not less than 10% and not more than 18% of total protein. It is intended for intramuscular or subcutaneous injection. It is obtained from the pooled plasma collected from at least 1000 donors who must be healthy and as far as can be ascertained be free from detectable agents of infection transmissible by transfusion of blood or blood components. No antibacterial is added to the plasma used. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. Multidose, but not single dose, preparations contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 5.0 to 7.2. 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 an airtight, colourless, glass container.

Ph. Eur. 8: (Human Normal Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Normale ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG); other proteins may be present and the total protein content is not less than 3%. It contains IgG antibodies of normal subjects; the standard does not apply to products intentionally prepared to contain fragments or chemically modified IgG. It is prepared as a stabilised solution and passed through a bacteria-retentive filter. It does not contain an antimicrobial preservative. The pH of a solution in sodium chloride 0.9% containing 1% of protein is 4.0 to 7.4. Storage requirements are similar to those for Human Normal Immunoglobulin, except that the freeze-dried preparation is stored in an airtight container at a temperature not exceeding 25 degrees.

USP 36: (Immune Globulin). A sterile solution of globulins that contains many antibodies normally present in human adult blood. It is prepared from pooled material (approximately equal quantities of blood, plasma, serum, or placentas) from not fewer than 1000 donors. It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It is intended for intramuscular injection. It contains glycine as a stabiliser, and a suitable preservative. It contains antibodies against diphtheria, measles, and poliomyelitis. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Normal immunoglobulin is available as two distinct preparations and formulations:

- an *intramuscular* injection (Human Normal Immunoglobulin (Ph. Eur. 8) and Immune Globulin (USP 36)) generally containing 16% of protein is used for passive immunisation, and sometimes also for primary antibody deficiencies
- the preparation formulated for *intravenous* use (Human Normal Immunoglobulin for Intravenous Administration (Ph. Eur. 8)) is used in disorders such as primary and secondary antibody deficiencies, as an immunomodulatory agent for immune thrombocytopenia, and to treat chronic inflammatory and immune-mediated diseases; solutions generally contain about 3 to 6% of protein, although some may contain up to 12%

Doses of normal immunoglobulin often appear confusing, being expressed variously in terms of weight (protein or immunoglobulin G content) or in terms of volume to be given, and the two do not always appear to correspond. It should be remembered that there may be differences between intravenous preparations of normal immunoglobulin including differing IgA content and IgG subclass distribution.

Normal immunoglobulin, being derived from the pooled plasma of blood donors, contains antibodies to bacteria and viruses currently prevalent in the general population; in the UK, and also in some other countries, typical antibodies

The symbol † denotes a preparation no longer actively marketed

present include those against hepatitis A, measles, mumps, rubella, and varicella. Normal immunoglobulin therefore may be used to provide passive immunisation against such diseases.

Normal immunoglobulin may be used to control outbreaks of **hepatitis A**, the recommended intramuscular dose for close contacts being 250 mg in those under 10 years of age and 500 mg in older children and adults. It may also be used for prophylaxis against hepatitis A in immunocompromised patients if their response to hepatitis A vaccine is unlikely to be adequate.

Normal immunoglobulin may be used to prevent or possibly modify an attack of **measles** in children and adults at special risk (such as those who are immunocompromised) but should be given as soon as possible after contact with measles. In the UK recommended doses, given intramuscularly, for the prevention or attenuation of an attack are 250 mg for those under 1 year of age, 500 mg for those aged 1 to 3 years, and 750 mg for those aged 3 years and over.

Normal immunoglobulin does not prevent **rubella** infection and is not recommended for the protection of pregnant women exposed to rubella; it should only be considered where termination of pregnancy is unacceptable. The dose is 750 mg by intramuscular injection.

Normal immunoglobulin may be used in the management of patients with **primary antibody deficiencies** such as congenital agammaglobulinaemia, hypogammaglobulinaemia, or **immunocompromised patients** including those with immunodeficiency syndromes; the immunoglobulin is given to provide protection against infectious diseases that such patients may suffer. The intramuscular preparation has been used but the intravenous route is usually preferred as it is less painful for the doses required. Alternatively, the subcutaneous route may be used. For intravenous infusion the dose, expressed in terms of weight (protein or immunoglobulin G content), is usually 400 to 800 mg/kg initially, then 200 mg/kg every 3 weeks adjusted as necessary according to trough-immunoglobulin concentrations: the maintenance dose is usually 200 to 800 mg/kg per month. In patients with secondary immunodeficiency syndromes, doses of 200 to 400 mg/kg every 3 to 4 weeks have been recommended. Other dosage regimens have been used. Subcutaneous doses are 200 to 500 mg/kg as an initial loading dose (divided over several days), followed by maintenance doses at repeated intervals to achieve a cumulative monthly dose of 400 to 800 mg/kg. When infused intravenously, normal immunoglobulin should always be given very carefully and slowly with gradual increases in the rate of infusion.

For prophylaxis of infection after **bone marrow transplantation**, normal immunoglobulin is given intravenously in a dose of 500 mg/kg weekly, adjusted according to response.

Intravenous infusion of normal immunoglobulin is also used to raise the platelet count in patients with **immune thrombocytopenia** (idiopathic thrombocytopenic purpura). Doses of 400 mg/kg are given daily for 2 to 5 consecutive days. Alternatively, a dose of 800 to 1000 mg/kg may be given on day 1 and repeated within 3 days if necessary. Further doses may be given as necessary.

For **Kawasaki disease**, normal immunoglobulin (used with aspirin) is given intravenously in a dose of 1.6 to 2 g/kg in divided doses over 2 to 5 days, or 2 g/kg given as a single dose. Similar doses of intravenous normal immunoglobulin have been tried in a range of disorders believed to have an auto-immune origin. The precise mode of action of normal immunoglobulin in such disorders is unknown.

For the treatment of **Guillain-Barré syndrome**, normal immunoglobulin is given intravenously in a dose of 400 mg/kg for 5 consecutive days, repeated every 4 weeks if required.

References.
1. Anonymous. Intravenous immunoglobulin (IVIG). *Med Lett Drugs Ther* 2006; 48: 101–3.
2. Gürcan HM, Ahmed AR. Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders. *Ann Pharmacother* 2007; 41: 812–23.
3. Provan D, *et al.* UK Immunoglobulin Expert Working Group. Prescribing intravenous immunoglobulin: summary of Department of Health guidelines. *BMJ* 2008; 337: 990–2.
4. Anonymous. I.V. immunoglobulin therapy for infectious diseases. *Drug Ther Bull* 2010; 48: 57–60.

Administration. Oral dosage with normal immunoglobulins has been proposed to reduce the incidence and severity of gastrointestinal infections, particularly in patients with defective immune systems including neonates. Although the main immunoglobulin secreted into the gastrointestinal tract in subjects with a normal immune system is IgA, which is not present in large quantities in commercial normal immunoglobulins, beneficial responses, especially in viral infections, have been reported after oral use. Systematic reviews have not, however, supported routine use of oral immunoglobulin for the prevention or treatment of gastrointestinal infections.[1-3] Preparations of immunoglobulin A are available in some countries and have been tried, mainly in bacterial gastrointestinal infections.[4,5]

1. Mohan P, Haque KN. Oral immunoglobulin for the prevention of rotavirus infection in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
2. Mohan P, Haque KN. Oral immunoglobulin for the treatment of rotavirus diarrhoea in low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 22/03/05).
3. Foster JP, Cole MJ. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/03/05).
4. Tjellström B, *et al.* Oral immunoglobulin A supplement in treatment of Clostridium difficile enteritis. *Lancet* 1993; 341: 701–2.
5. Hammarström V, *et al.* Oral immunoglobulin treatment in Campylobacter jejuni enteritis. *Lancet* 1993; 341: 1036.

Blood disorders. Intravenous normal immunoglobulins are used in the treatment of symptomatic severe immune thrombocytopenia (p. 1606.1). Other blood disorders in which normal immunoglobulins have been tried include agranulocytosis[1] and haemolytic disease of the newborn (p. 2377.2), haemolytic anaemias (p. 1122.2), red cell aplasia caused by parvovirus B19 infections (see under Passive Immunisation, p. 2406.3), thrombotic thrombocytopenic purpura and haemolytic-uraemic syndrome (see Thrombotic Microangiopathies p. 1159.1), and thrombocytopenia with a variety of causes.[2-10]

1. Fasth A. Immunoglobulin for neonatal agranulocytosis. *Arch Dis Child* 1986; 61: 86–7.
2. Hoffman DM, *et al.* Human immunodeficiency virus-associated thrombocytopenia. *DICP Ann Pharmacother* 1989; 23: 157–160.
3. Frame JN, *et al.* Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 1989; 111: 946–7.
4. Howrie DL, *et al.* Use of iv immune globulin for treatment of phenytoin-induced thrombocytopenia. *Clin Pharm* 1989; 8: 734–7.
5. Landonio G, *et al.* HIV-related severe thrombocytopenia in intravenous drug users: prevalence, response to therapy in a medium-term follow-up, and pathogenic evaluation. *AIDS* 1990; 4: 29–34.
6. Goulder P, *et al.* Intravenous immunoglobulin in virus associated haemophagocytic syndrome. *Arch Dis Child* 1990; 65: 1275–7.
7. Larner AJ, *et al.* Life threatening thrombocytopenia in sarcoidosis: response to vincristine, human immunoglobulin, and corticosteroids. *BMJ* 1990; 300: 317–19.
8. Ray JB, *et al.* Intravenous immune globulin for the treatment of presumed quinidine-induced thrombocytopenia. *DICP Ann Pharmacother* 1990; 24: 693–5.
9. Salzman MB, Smith EM. Phenytoin-induced thrombocytopenia treated with intravenous immune globulin. *J Pediatr Hematol Oncol* 1998; 20: 152–3.
10. Majluf-Cruz A, *et al.* Usefulness of a low-dose intravenous immunoglobulin regimen for the treatment of thrombocytopenia associated with AIDS. *Am J Hematol* 1998; 59: 127–32.

Bowel disorders. Intravenous normal immunoglobulin may be beneficial[1-3] in inducing remission of Crohn's disease and ulcerative colitis and in antibiotic-associated or pseudomembranous colitis associated with *Clostridium difficile* infection.[4,5]

1. Rohr G, *et al.* Treatment of Crohn's disease and ulcerative colitis with 7S-immunoglobulin. *Lancet* 1987; i: 170.
2. Knoflach P, *et al.* Crohn disease and intravenous immunoglobulin G. *Ann Intern Med* 1990; 112: 385–6.
3. Körber J, *et al.* A case of Crohn's disease with increased CD8 T-cell activation and remission during therapy with intravenous immunoglobulins. *Scand J Gastroenterol* 1998; 33: 1113–17.
4. Leung DYM, *et al.* Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. *J Pediatr* 1991; 118: 633–7.
5. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother* 2004; 53: 882–4.

Complex regional pain syndrome. It has been suggested that the immune system may be involved in sustaining complex regional pain syndrome (CRPS—p. 8.1) and a small double-blind crossover pilot study in patients who had CRPS for between 6 and 30 months that was refractory to standard treatment suggested that low-dose intravenous normal immunoglobulin (250 mg/kg daily on 2 consecutive days) could substantially reduce the intensity of pain and improve autonomic limb symptoms.[1]

1. Goebel A, *et al.* Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. *Ann Intern Med* 2010; 152: 152–8.

Epilepsy. Normal immunoglobulins have sometimes been of benefit[1-3] in the treatment of children with intractable epilepsy, including Lennox-Gastaut syndrome or West's syndrome, but a review of the literature found that few well controlled studies had been conducted,[4] and a Canadian evidence-based guideline recommended against its use.[5] Although a positive trend in favour of intravenous immunoglobulin therapy for refractory epilepsy was noted in one double-blind controlled study[6] involving 61 patients, the results were not considered to be statistically significant.

1. Aritzumi M, *et al.* High dose gammaglobulin for intractable childhood epilepsy. *Lancet* 1983; ii: 162–3.
2. Sandstedt P, *et al.* Intravenous gammaglobulin for post-encephalitic epilepsy. *Lancet* 1984; ii: 1154–5.
3. van Engelen BGH, *et al.* High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome: an add-on study. *Eur J Pediatr* 1994; 153: 762–9.
4. Duse M, *et al.* Intravenous immune globulin in the treatment of intractable childhood epilepsy. *Clin Exp Immunol* 1996; 104 (suppl 1): 71–6.
5. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; 21 (suppl 1): S57–S107.
6. van Rijckevorsel-Harmant K, *et al.* Treatment of refractory epilepsy with intravenous immunoglobulins: results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994; 24: 162–6.

Hypogammaglobulinaemia. See under Primary Antibody Deficiency, below.

Immunocompromised patients. Immunodeficiency states may arise from primary disorders of the immune system, or, more commonly, they are secondary to immunosuppressive therapy, HIV infection, or haematological malignancies. Premature neonates may have deficits in their immune systems due to their immaturity; placental transfer of maternal antibodies usually occurs after about 32 weeks of gestation. Such patients and neonates may be deficient in gammaglobulins and they could potentially benefit from the use of normal immunoglobulins to address their increased susceptibility to infection. For information on the use of immunoglobulins in specific conditions, see the following sections and under Neonatal Infection, p. 2406.2.

MALIGNANCIES. Hypogammaglobulinaemia and the effects of treatment may increase the susceptibility to infection of patients with *chronic lymphocytic leukaemia*.[1] In a study[2] of 81 patients with chronic lymphocytic leukaemia considered to be at an increased risk of infection, intravenous normal immunoglobulin 400 mg/kg given every 3 weeks for one year reduced the incidence of bacterial infection compared with saline placebo. The incidence of viral and fungal infections was not affected. A study in 34 patients[3] suggested that a dose of normal immunoglobulin 250 mg/kg per month was adequate for routine prophylaxis in most patients. Beneficial effects on infection rates have been reported in patients with *multiple myeloma* receiving normal immunoglobulins.[4] A systematic review[5] concluded that there was no benefit in terms of mortality in patients with lymphoproliferative disorders given prophylactic normal immunoglobulin, but that there was a substantial reduction in infections which might justify such use.

1. Wierda WG. Immunologic monitoring in chronic lymphocytic leukaemia. *Curr Oncol Rep* 2003; 5: 419–25.
2. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. *N Engl J Med* 1988; 319: 902–7.
3. Chapel H, *et al.* Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994; 88: 209–12.
4. Chapel HM, *et al.* Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. *Lancet* 1994; 343: 1059–63.
5. Raanani P, *et al.* Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/02/10).

PRIMARY ANTIBODY DEFICIENCY. There are 3 major forms of primary antibody deficiency (primary immune deficiency): X-linked agammaglobulinaemia (XLA, Bruton's agammaglobulinaemia), common variable immunodeficiency (CVID) which includes IgG subclass and specific antibody deficiencies, and selective IgA deficiency. The disease is characterised by a wide range of infective complications as well as auto-immune disorders. Management is by replacement therapy with normal immunoglobulin accompanied by appropriate antimicrobial therapy for breakthrough infections.[1-5] Immunisation against infection is of little value (although some patients with CVID may occasionally respond)[5] and is contra-indicated for live viral vaccines.

Normal immunoglobulin was traditionally given by the intramuscular route. However, the maximum dose that could be reasonably given by this route was 25 mg/kg weekly, and it was therefore only satisfactory for patients with mild disease.[6] The introduction of intravenous preparations of normal immunoglobulin allowed high doses to be used in those with severe disease. This route should therefore be used for all patients with XLA and for patients with CVID who have more than mild disease.[1] The use of intravenous normal immunoglobulin in IgG subclass deficiency, with or without IgA deficiency, or in specific antibody deficiency is successful, though less well established. The dose and frequency of administration of intravenous normal immunoglobulin is variable and should be adjusted to prevent breakthrough infection. It has been suggested that different normal immunoglobulin products may not be equivalent; however, a Canadian guideline considered that they could be used interchangeably from the standpoint of efficacy, although individual patients might have fewer adverse reactions to a particular product, and be unwilling to change.[5] Most patients require 200 to 600 mg/kg every 2 or 3 weeks to maintain optimum protection.[6] In one study,[7] doses of between 260 and

1120 mg/kg every 3 weeks were necessary to maintain residual serum IgG concentrations above 500 mg/dL. These doses were found to be effective in reducing the incidence of severe acute bacterial infections and pulmonary insufficiency in children with XLA. Surgical procedures should be covered with additional normal immunoglobulin and appropriate prophylactic antibacterials. Home treatment with intravenous normal immunoglobulin has been used successfully in several countries in both adults and children.[5,6,8-11] Adverse reactions have been few and generally mild.[6,9,10] They are most likely to occur during the first infusion and during intercurrent illness, and may be precipitated by a high infusion rate.[11] Long-term treatment of children with antibody deficiencies with intravenous normal immunoglobulin has been shown to lead to normal growth and similar rates of infection to those found in non-immunodeficient children.[12]

Immunoglobulin replacement can alternatively be given by subcutaneous infusion as an alternative to intravenous therapy.[2,4,13,14] Subcutaneous use is considered as effective as intravenous in protecting against infection, and may be more convenient for giving at home, although evidence of equivalence is lacking for patients with severe autoimmune symptoms. A suggested starting dose in most patients is 100 to 150 mg/kg weekly.[5] The intraventricular route has been of benefit in some patients with echovirus encephalitis.[6,15]

1. Carrock Sewell WA, *et al.* Therapeutic strategies in common variable immunodeficiency. *Drugs* 2003; 63: 1359–71.
2. Schwartz SA. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am* 2000; 47: 1355–69.
3. Empson M, *et al.* The assessment and management of primary antibody deficiency. *N Z Med J* 2004; 117: U914.
4. Durandy A, *et al.* Immunoglobulin replacement therapy in primary antibody deficiency diseases—maximizing success. *Int Arch Allergy Immunol* 2005; 136: 217–29.
5. Shehata N, *et al.* The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. *Transfus Med Rev* 2010; 24 (suppl 1): S28–S50.
6. Spickett GP, *et al.* Primary antibody deficiency in adults. *Lancet* 1991; 337: 281–4.
7. Quartier P, *et al.* Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; 134: 589–96.
8. Ochs HD, *et al.* Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. *Lancet* 1986; i: 610–11.
9. Ryan A, *et al.* Home intravenous immunoglobulin therapy for patients with primary hypogammaglobulinaemia. *Lancet* 1988; ii: 793.
10. Kobayashi RH, *et al.* Home self-administration of intravenous immunoglobulin therapy in children. *Pediatrics* 1990; 85: 705–9.
11. Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. *BMJ* 1994; 308: 581–5.
12. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973-93. *Arch Dis Child* 1996; 74: 527–30.
13. Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. *BioDrugs* 2007; 21: 105–16.
14. Hefbert M, Farragher A. Subcutaneous immunoglobulin for patients with antibody deficiency. *Br J Hosp Med* 2007; 68: 206–10.
15. Erlendsson K, *et al.* Successful reversal of echovirus encephalitis in x-linked hypogammaglobulinemia by intraventricular administration of immunoglobulin. *N Engl J Med* 1985; 312: 351–3.

TRANSPLANTATION. Normal immunoglobulin may be used in patients undergoing haematopoietic stem cell transplantation (HSCT—see p. 1933.1) with the aim of decreasing the incidence of bacterial and of symptomatic CMV infection, and that of graft-versus-host disease.[1,2] A 1990 National Institutes of Health consensus considered that intravenous normal immunoglobulin was useful for both purposes in these immunosuppressed patients.[3] However, later results have not tended to support this. Reviews and meta-analyses have concluded that there is little evidence to support any benefit of normal immunoglobulin in reducing infection,[1,2,4] or all-cause mortality.[4] Although there is some evidence to suggest that the risk of interstitial pneumonitis may be reduced, this seems to be counterbalanced by an increased risk of hepatic veno-occlusive disease.[4] Evidence for any benefit in reducing graft-versus-host disease is at best equivocal[1] or absent.[4] It has been concluded therefore, that normal immunoglobulin does not have a role for routine prophylaxis in HSCT.[2,4]

Normal immunoglobulin is also increasingly used in the setting of solid organ transplantation. A Canadian evidence-based guideline[5] concluded that there was sufficient evidence to support its use in renal transplantation where the patient would receive a kidney from a living donor to whom he or she was sensitised, and for use after plasmapheresis in patients with acute antibody-mediated rejection. There was insufficient evidence to support use in cardiac, liver, or lung transplantation.

1. Sokos DR, *et al.* Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2002; 8: 117–30.
2. Raanani P, *et al.* Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/02/10).
3. NIH. Intravenous immunoglobulin: prevention and treatment of disease. *NIH Consens Statement Online* 1990; 8: 1–23. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hsnihcdc6&part=A7621 (accessed 24/02/10)
4. Raanani P, *et al.* Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. *J Clin Oncol* 2009; 27: 770–81.
5. Shehata N, *et al.* The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. *Transfus Med Rev* 2010; 24 (suppl 1): S7–S27.

Kawasaki disease. Kawasaki disease, also known as mucocutaneous lymph node syndrome of childhood, occurs mainly in children under 5 years of age. It is epidemic and endemic worldwide but is a particular problem in Japan. Kawasaki disease presents with high fever which persists for at least 5 days and may be followed by bilateral conjunctivitis, changes in the oropharyngeal mucosa, signs of vasculitis in the extremities, rash, and cervical lymphadenopathy. The major complications of Kawasaki disease are cardiac effects including coronary artery aneurysm, aortic or mitral incompetence, myocarditis, and pericarditis with effusion. The cause of the disease is unknown, although an infective aetiology has been suggested. Early diagnosis, expert cardiac assessment, and immediate treatment are essential for improved outcome.

Treatment aims to reduce inflammation, particularly in the coronary arterial wall and myocardium, and therefore prevent the development of cardiac complications. Long-term antiplatelet treatment is given as necessary to prevent coronary thrombosis.

Initial treatment is with aspirin and normal immunoglobulin.[1-3] Despite the anti-inflammatory and antiplatelet properties of aspirin it does not appear to lower the incidence of coronary abnormalities in Kawasaki disease when used alone; however, high-dose aspirin and intravenous high-dose normal immunoglobulin appear to possess an additive anti-inflammatory effect when used together and a decreased incidence of coronary-artery abnormalities has been found after such a combination as compared with aspirin alone. Treatment should begin if possible within 10, and preferably within 7, days of the onset of illness. Treatment before day 5 appears to offer no more advantage in preventing cardiac sequelae than treating from days 5 to 7, but it may be associated with an increased need for re-treatment with normal immunoglobulin. Treatment should be given to children presenting after the tenth day of illness if they have either persistent unexplained fever or aneurysms with ongoing systemic inflammation.[2]

Normal immunoglobulin has been given by intravenous infusion in divided doses over 2 to 5 days, but high-dose administration as a single dose is now recommended; a meta-analysis[4] and a systematic review[5] have concluded that single-dose therapy is associated with a lower incidence of coronary abnormalities after 30 days than multiple-dose treatment. The optimum dosage and duration of treatment with aspirin is unknown, but the usual practice is to use an anti-inflammatory regimen until the fever has settled and then to convert to an antithrombotic regimen. A few patients fail to respond to treatment with aspirin and normal immunoglobulin. Re-treatment with normal immunoglobulin may be considered for those with persistent or recurring fever.[2,6]

Evidence for the use of corticosteroids remains inconclusive.[1] They have been given in some centres[7] but since the introduction of immunoglobulin therapy they have not been routinely used as there is a risk that they may exacerbate coronary artery aneurysms. Nevertheless, their use has received renewed attention; randomised studies comparing the adjunctive use of corticosteroids with standard therapy alone have suggested they may be of benefit.[8-10] Corticosteroids have also been tried as an alternative to a second course of intravenous normal immunoglobulin, and a study[11] reported that intravenous pulse corticosteroid treatment was as effective as a second course of normal immunoglobulin. However, most experts do not use them unless fever continues after the second course of normal immunoglobulin.[2]

Alternative suggested drugs for patients refractory to normal immunoglobulin include ulinastatin,[12] which has been used for adjunctive therapy in Japan, but its efficacy remains currently unproven. Abciximab has been used to treat patients with large coronary aneurysms; in one study,[13] patients given abciximab in addition to standard therapy showed a greater regression in aneurysm diameter. Other treatments that have been tried in patients unresponsive to initial normal immunoglobulin include pentoxifylline,[2] the use of cyclophosphamide with corticosteroids in particularly refractory cases,[2] and infliximab;[14,15] an analysis of treatment of resistant Kawasaki disease in the United States between 2001 and 2006 noted a trend towards the increased use of infliximab.[16]

Long-term management. Low-dose aspirin is commonly continued for about 6 weeks after the onset of illness and then stopped if there are no coronary abnormalities.[1,2] Some practitioners use aspirin and dipyridamole as antithrombotic therapy although it is unknown whether this provides benefit over aspirin alone. Dipyridamole may be used as an alternative antithrombotic agent for patients who cannot tolerate aspirin. Aspirin is usually continued for at least one year if coronary abnormalities are present and should be continued indefinitely if coronary aneurysms persist. Anticoagulation with warfarin or heparin in addition to aspirin may be necessary in some patients such as those with giant or multiple aneurysms.

1. Harnden A, *et al.* Kawasaki disease. *BMJ* 2009; 338: 1133–8.
2. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; 114: 1708–33. Correction. *ibid.* 2005; 115: 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 25/05/06) Also published in *Circulation* 2004; 110: 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
3. Wood LE, Tulloh RM. Kawasaki disease in children. *Heart* 2009; 95: 787–92.
4. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; 96: 1057–61.
5. Oates-Whitehead RM, *et al.* Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/03/05).
6. Sundel RP, *et al.* Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993; 123: 657–9.
7. Shinohara M, *et al.* Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999; 135: 465–9.
8. Sundel RP, *et al.* Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003; 142: 611–16.
9. Okada Y, *et al.* Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003; 143: 363–7.
10. Wooditch AC, Aronoff SC. Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children. *Pediatrics* 2005; 116: 989–95.
11. Furukawa T, *et al.* Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. *Arch Dis Child* 2008; 93: 142–6.
12. Zaitsu M, *et al.* Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. *J Infect Dis* 2000; 181: 1101–9.
13. Williams RV, *et al.* Does abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Abstract: *Pediatrics* 2002; 109: 132. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/1/e4 (accessed 24/03/05)
14. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; 146: 662–7.
15. Burns JC, *et al.* Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008; 153: 833–8.
16. Son MB, *et al.* Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics* 2009; 124: 1–8.

Kidney disorders. Treatment with normal immunoglobulin has been of benefit in some patients with haemolytic-uraemic syndrome and in those with lupus nephritis (see under Musculoskeletal and Nerve Disorders, below). For mention of the use of normal immunoglobulin in IgA nephropathy, see Glomerular Kidney Disease, p. 1604.3.

Musculoskeletal and nerve disorders. High-dose intravenous normal immunoglobulin has been tried with some benefit in various disorders of the nerves, muscles, joints, and connective tissues which may have an auto-immune basis.[1] These include multiple sclerosis,[2-4] chronic inflammatory demyelinating polyneuropathy,[5,6] polymyositis and dermatomyositis,[7-12] myasthenia gravis,[13-17] stiff-man syndrome,[18-22] chronic systemic juvenile arthritis,[23-25] SLE[26] including lupus nephritis,[27] Guillain-Barré syndrome (see p. 2406.1), and motor neurone disease (see also p. 2406.1). It is also being investigated in Alzheimer's disease.[28] Guidelines issued by an expert committee in Canada[29] included recommendations on the use and dose of normal immunoglobulin for acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis and polymyositis, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome and myasthenia gravis, multifocal motor neuropathy, multiple sclerosis, opsoclonus-myoclonus, neuropsychiatric disorders associated with streptococcal infections in children, short-term management of Rasmussen's encephalitis, and stiff man syndrome.

1. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; 291: 2367–75.
2. Fazekas F, *et al.* Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997; 349: 589–93.
3. Hommes OR, *et al.* Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* 2004; 364: 1149–56.
4. Achiron A, *et al.* Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2004; 61: 1515–20.
5. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002; 59 (suppl 6): S13–S21.
6. Brannagan TH. Intravenous gammaglobulin (IVIg) for treatment of CIDP and related immune-mediated neuropathies. *Neurology* 2002; 59 (suppl 6): S33–S40.
7. Cherin P, *et al.* Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. *Am J Med* 1991; 91: 162–8.
8. Lang BA, *et al.* Treatment of dermatomyositis with intravenous gammaglobulin. *Am J Med* 1991; 91: 169–72.
9. Dalakas MC, *et al.* A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; 329: 1993–2000.
10. Brownell AKW. Intravenous immune globulin for dermatomyositis. *N Engl J Med* 1994; 330: 1392.

11. Collet E, *et al.* Juvenile dermatomyositis: treatment with intravenous gammaglobulin. *Br J Dermatol* 1994; 130: 231–4.
12. Cherin P, *et al.* Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum* 2002; 46: 467–74.
13. Bassan H, *et al.* High-dose intravenous immunoglobulin in transient neonatal myasthenia gravis. *Pediatr Neurol* 1998; 18: 181–3.
14. Jongen JLM, *et al.* High-dose intravenous immunoglobulin therapy for myasthenia gravis. *J Neurol* 1998; 245: 26–31.
15. Howard JF. Intravenous immunoglobulin for the treatment of acquired myasthenia gravis. *Neurology* 1998; 51 (suppl 5): S30–S36.
16. Selcen D, *et al.* High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. *Pediatr Neurol* 2000; 22: 40–3.
17. Zinman L, *et al.* IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology* 2007; 68: 837–41.
18. Karlson EW, *et al.* Treatment of stiff-man syndrome with intravenous immune globulin. *Arthritis Rheum* 1994; 37: 915–18.
19. Amato AA, *et al.* Treatment of stiff-man syndrome with intravenous immunoglobulin. *Neurology* 1994; 44: 1652–4.
20. Barker RA, Marsden CD. Successful treatment of stiff man syndrome with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1997; 62: 426–7.
21. Khanlou H, Elger G. Long-term remission of refractory stiff-man syndrome after treatment with intravenous immunoglobulin. *Mayo Clin Proc* 1999; 74: 1231–2.
22. Dalakas MC, *et al.* High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* 2001; 345: 1870–6.
23. Groothoff JW, van Leeuwen EF. High dose intravenous gammaglobulin in chronic systemic juvenile arthritis. *BMJ* 1988; 296: 1362–3.
24. Giannini EH, *et al.* Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. *J Rheumatol* 1996; 23: 919–24.
25. Uziel Y, *et al.* Intravenous immunoglobulin therapy in systemic onset juvenile rheumatoid arthritis: a followup study. *J Rheumatol* 1996; 23: 910–18.
26. Francioni C, *et al.* Long term IV Ig treatment in systemic lupus erythematosus. *Clin Exp Rheumatol* 1994; 12: 163–8.
27. Lin C-Y, *et al.* Improvement of histological and immunological change in steroid and immunosuppressive drug-resistant lupus nephritis by high-dose intravenous gamma globulin. *Nephron* 1989; 53: 303–10.
28. Dodel R, *et al.* Intravenous immunoglobulins as a treatment for Alzheimer's disease: rationale and current evidence. *Drugs* 2010; 70: 513–28.
29. Feasby T, *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; 21 (suppl 1): S57–S107.

GUILLAIN-BARRÉ SYNDROME. Guillain-Barré syndrome[1,2] (acute idiopathic inflammatory polyneuropathy; acute idiopathic demyelinating neuropathy; acute infectious polyneuropathy) may follow an infection or, more rarely, immunisation, but very often no predisposing factor can be identified. An association with infection with *Campylobacter jejuni* is frequent,[2,3] but the syndrome is also commonly associated with infection with CMV, Epstein-Barr virus, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*.[1,2] Reversible demyelination results in pain and progressive flaccid paralysis. An auto-immune aetiology seems likely. Severely affected patients require cardiovascular monitoring and respiratory support if respiratory muscles are affected or autonomic instability is present. Corticosteroids have been given but are generally considered to be of little value.[2,4] Plasma exchange (see p. 1158.3) is effective if given early,[5] but is not universally available and is not suitable for all patients. Intravenous normal immunoglobulin, again ideally given within 2 weeks of onset, has therefore become the treatment of choice in many centres.[2] A systematic review[6] has concluded that use of normal immunoglobulins is at least as effective as plasma exchange, but that there is no advantage from combining the two forms of treatment. Deterioration has also been noted in some patients after immunoglobulin therapy,[7,8] although one study[9] found that the incidence of relapse was greater after plasma exchange than after normal immunoglobulin.

1. Kuwabara S. Guillain Barré syndrome: epidemiology, pathophysiology and management. *Drugs* 2004; 64: 597–610.
2. van Doorn PA, *et al.* Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurol* 2008; 7: 939–50.
3. Rees JH, *et al.* Campylobacter jejuni infection and Guillain-Barré syndrome. *N Engl J Med* 1995; 333: 1374–9.
4. Hughes RAC, *et al.* Corticosteroids for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 27/08/10).
5. Raphaël JC, *et al.* Plasma exchange for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 29/03/05).
6. Hughes RAC, *et al.* Intravenous immunoglobulin for Guillain-Barré syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 05/08/10).
7. Irani DN, *et al.* Relapse in Guillain-Barré syndrome after treatment with human immune globulin. *Neurology* 1993; 43: 872–5.
8. Castro LHM, Ropper AH. Human immune globulin infusion in Guillain-Barré syndrome: worsening during and after treatment. *Neurology* 1993; 43: 1034–6.
9. Romano JG, *et al.* Relapses in the Guillain-Barré syndrome after treatment with intravenous immune globulin or plasma exchange. *Muscle Nerve* 1998; 21: 1327–30.

MOTOR NEURONE DISEASE. Several studies and a systematic review have shown normal immunoglobulins to be of benefit in the treatment of multifocal motor neuropathy, a form of motor neurone disease (p. 2605.2) associated with anti-GM_1 antibody formation.[1-7] In most patients, however, improvement has to be maintained with periodic infusion and some become less responsive to therapy over time, requiring higher doses. A retrospective study[8] of 10 patients with multifocal motor neuropathy treated with normal immunoglobulins showed that while the initial response could be maintained for several years, efficacy decreased during prolonged treatment even when doses were progressively adjusted. During the first few years of therapy, increased dosage restored the efficacy of normal immunoglobulins, but was found to be less able to do so later in follow-up.

1. Van den Berg LH, *et al.* Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; 59: 248–52.
2. Meucci N, *et al.* Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 1997; 63: 765–9.
3. Van den Berg LH, *et al.* The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. *Brain* 1998; 121: 421–8.
4. Ellis CM, *et al.* Use of human intravenous immunoglobulin in lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 1999; 67: 15–19.
5. Federico P, *et al.* Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000; 55: 1256–62.
6. Léger JM, *et al.* Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; 124: 145–53.
7. van Schaik IN, *et al.* Intravenous immunoglobulin for multifocal motor neuropathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 14/02/06).
8. Terenghi F, *et al.* How long is IVIg effective in multifocal motor neuropathy? *Neurology* 2004; 62: 666–8.

Neonatal disorders. *HAEMOLYTIC DISEASE OF THE NEWBORN.* For a discussion of haemolytic disease of the newborn and its management, including the use of intravenous immunoglobulin as an alternative to exchange transfusions in affected pregnancies, see p. 2377.2.

NEONATAL INFECTION. Sepsis is a serious problem in premature infants despite appropriate antimicrobial therapy. Preterm infants are born with low serum-immunoglobulin concentrations that decrease over the next several weeks of life. There is also a deficiency of antibodies to specific organisms such as group B streptococci, *Staphylococcus epidermidis*, and *Escherichia coli*.

Some, but not all, studies suggest that prophylactic use of intravenous normal immunoglobulin in premature infants shortly after birth can decrease the incidence of septicaemia.[1] Aspects of the methodology of these studies have, however, been criticised[2] and a systematic review[3] concluded that prophylactic use of intravenous immunoglobulin for prevention of infection in preterm or low birthweight neonates was of at best marginal benefit only, and of no benefit in preventing sepsis, and did not recommend routine use. Some benefit has been seen after use of intravenous immunoglobulin to treat infants with suspected sepsis[1] and it may improve the response to antibacterials,[4] although a further systematic review[5] found insufficient evidence to support routine use in infants with suspected, or subsequently proved, neonatal infection.

The optimum dosage of intravenous immunoglobulin is not established. A prophylactic dose of 500 mg/kg on admission repeated every 1 to 2 weeks has been suggested for units where infection is common in very low birthweight infants.[1] Others have suggested adjusting the dose to maintain a specified serum-immunoglobulin concentration. Alternatively, normal immunoglobulin could be given only to infants with immunoglobulin concentrations below a certain level, or be reserved for immediate use in those who become ill with suspected sepsis.[1]

Normal immunoglobulin cannot protect against all types of infection. Normal immunoglobulin preparations from different manufacturers may have, for a specific pathogen, differing levels of specific antibody and differing levels of functional activity or there may be lot-to-lot variability in functional activity for normal immunoglobulin from a specific manufacturer. Such variability, resulting in low concentrations of functional antibodies in the 4 batches of immunoglobulins used in the National Institute of Child Health Study,[6] was held responsible for the lack of demonstrable efficacy of immunoglobulins in that study, one of the largest to date.

1. Whitelaw A. Treatment of sepsis with IgG in very low birthweight infants. *Arch Dis Child* 1990; 65: 347–8.
2. Noya FJD, Baker CJ. Intravenously administered immune globulin for premature infants: a time to wait. *J Pediatr* 1989; 115: 969–71.
3. Ohlsson A, Lacy J. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 29/03/05).
4. Christensen RD, *et al.* Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991; 118: 606–14.
5. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 28/06/10).
6. Fanaroff AA, *et al.* A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. *N Engl J Med* 1994; 330: 1107–13.

Neuropsychiatric disorders. Benefit has been shown from plasma exchange or intravenous immunoglobulin in children with exacerbations of obsessive-compulsive disorder or tic disorders including Tourette's syndrome associated with streptococcal infection.[1] These results suggested that these disorders may respond to immunomodulatory therapy in a subgroup of patients with paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), believed to be due to cross-reaction of antistreptococcal antibodies with neural tissue. In a double-blind, placebo-controlled study[2] of the use of normal immunoglobulins in 30 patients with tic disorders, despite initial improvement compared with placebo over 8 weeks no significant differences were found in the severity of obsessions and compulsions beyond this time.

1. Perlmutter SJ, *et al.* Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; 354: 1153–8.
2. Hoekstra PJ, *et al.* Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry* 2004; 65: 537–42.

Passive immunisation. *CMV INFECTION.* See Transplantation, under Immunocompromised Patients, p. 2405.1.

HEPATITIS C. In a randomised, placebo-controlled study[1] in seronegative sexual partners of patients positive for antibody to hepatitis C, normal immunoglobulin given intramuscularly every 2 months was found to significantly reduce the incidence of subsequent seroconversion. One of 450 subjects who received normal immunoglobulin became seropositive during follow-up compared with 6 of 449 who had received placebo.

1. Piazza M, *et al.* Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin: a randomized controlled trial. *Arch Intern Med* 1997; 157: 1537–44.

PARVOVIRUS B19 INFECTION. Persistent infection with human parvovirus B19 can cause red cell aplasia with resultant anaemia, particularly in immunocompromised patients. Normal immunoglobulins contain antibodies able to neutralise parvovirus B19 and have been used in various groups of infected patients.[1] Resolution of anaemia and clearance of parvovirus B19 from the circulation have been reported after use of normal immunoglobulin in a patient who had had red cell aplasia for 10 years.[2] Normal immunoglobulin was given by intravenous infusion in a dose of 400 mg/kg daily for 10 days and then periodically for several months. Successful treatment of anaemia due to parvovirus B19-induced red cell aplasia with plasmapheresis and intravenous immunoglobulin has been described in a liver transplant recipient.[3] Efficacy has also been found in recipients of other solid-organ transplants including heart, kidney, and lung.[1] Clearance of parvovirus B19 from the circulation has been reported in patients who also have AIDS, but the presence of concomitant opportunistic infections may prevent resolution of the anaemia.[4,5]

Normal immunoglobulin given to patients with parvovirus B19-associated chronic fatigue syndrome has also resulted in clearance of the virus from the circulation and resolution of symptoms.[6,7]

Beneficial responses to intravenous immunoglobulin have also been reported in a few patients with parvovirus B19 infections associated with vasculitic syndromes.[8,9]

1. Mouthon L, *et al.* Intravenous immunoglobulins in autoimmune- or parvovirus B19-mediated pure red-cell aplasia. *Autoimmun Rev* 2005; 4: 264–9.
2. Kurtzman G, *et al.* Pure red-cell aplasia of 10 years' duration due to persistent parvovirus B19 infection and its cure with immunoglobulin therapy. *N Engl J Med* 1989; 321: 519–23.
3. Ramage JK, *et al.* Parvovirus B19-induced red cell aplasia treated with plasmapheresis and immunoglobulin. *Lancet* 1994; 343: 667–8.
4. Frickhofen N, *et al.* Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990; 113: 926–33.
5. Bowman CA, *et al.* Red cell aplasia associated with human parvovirus B19 and HIV infection: failure to respond clinically to intravenous immunoglobulin. *AIDS* 1990; 4: 1038–9.
6. Kerr JR, *et al.* Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003; 36: e100–e106. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/374666 (accessed 15/07/08)
7. McGhee SA, *et al.* Persistent parvovirus-associated chronic fatigue treated with high dose intravenous immunoglobulin. *Pediatr Infect Dis J* 2005; 24: 272–4.
8. Finkel TH, *et al.* Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; 343: 1255–8.
9. Viguier M, *et al.* Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. *N Engl J Med* 2001; 344: 1481–2.

TOXIC SHOCK SYNDROME. For a discussion of toxic shock syndrome and its treatment, including reference to improved survival after administration of intravenous normal immunoglobulins, see p. 209.3.

Pregnancy. Fetal loss has been attributed in some cases to the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin) in the mother. Successful pregnancy outcome has been reported after use of intravenous normal immunoglobulin during pregnancy to a few such women.[1]

1. Triolo G, *et al.* IVIG in APS pregnancy. *Lupus* 2004; 13: 731–5.

Skin disorders. Normal immunoglobulins have been tried in a few patients with blistering skin diseases.[1-3] The usual treatment for pemphigus and pemphigoid is with systemic corticosteroids; intravenous normal immunoglobulins in

high doses have produced generally transient improvement when used alone,[4] although corticosteroid-sparing effects have been reported.[5,6] Successful treatment with high doses of intravenous normal immunoglobulin plus rituximab has also been reported in some patients with refractory pemphigus vulgaris.[7] There have been case reports of patients with severe epidermolysis bullosa acquisita responding to therapy with high-dose intravenous immunoglobulins.[8,9] Studies have been conducted into the use of high-dose normal immunoglobulin for the treatment of other blistering conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.[10] One retrospective analysis[11] of 48 consecutive cases of toxic epidermal necrolysis found a beneficial effect with survival in 42 patients. In contrast, a prospective open study[12] in 34 consecutive patients admitted to hospital with Stevens-Johnson syndrome or toxic epidermal necrolysis suggested that normal immunoglobulin might actually be associated with an increase in mortality. Further retrospective analyses, however, did find a reduction in mortality in 16 consecutive patients admitted with toxic epidermal necrolysis[13] and in 7 children with Stevens-Johnson syndrome.[14] Normal immunoglobulin has also produced benefit in patients with pyoderma gangrenosum.[15-19]

Clinical benefit was noted in 9 of 10 patients with autoimmune chronic urticaria who were given a 5-day course of intravenous immunoglobulins, 2 of whom had prolonged remission over 3 years of follow-up.[20] Benefit has also occurred after high-dose intravenous immunoglobulin therapy for atopic dermatitis,[21] psoriasis,[22] and pityriasis rubra pilaris.[23] The cutaneous lesions in a young child with juvenile dermatomyositis were successfully treated with high-dose intravenous immunoglobulin.[24]

Intramuscular normal immunoglobulin has been used with some success either alone or in combination therapy for recalcitrant suppurative skin diseases such as hidradenitis suppurativa, folliculitis decalvans, or chronic recurrent furunculosis or follicultis.[25]

1. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; 140: 865–74.
2. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003; 139: 1051–9.
3. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006; 6: 557–78.
4. Godard W, *et al.* Bullous pemphigoid and intravenous gammaglobulin. *Ann Intern Med* 1985; 103: 965.
5. Beckers RCY, *et al.* Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. *Br J Dermatol* 1995; 133: 289–93.
6. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; 45: 825–35.
7. Ahmed AR, *et al.* Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; 355: 1772–9.
8. Mohr C, *et al.* Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol* 1995; 132: 824–6.
9. Gourgiotou K, *et al.* Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol* 2002; 16: 77–80.
10. Mittmann N, *et al.* Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. *Am J Clin Dermatol* 2006; 7: 359–68.
11. Prins C, *et al.* Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003; 139: 26–32.
12. Bachot N, *et al.* Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; 139: 33–6.
13. Trent JT, *et al.* Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. *Arch Dermatol* 2003; 139: 39–43.
14. Metry DW, *et al.* Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003; 112: 1430 6.
15. Dirschka T, *et al.* Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998; 39: 789–90.
16. Hagman JH, *et al.* The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosum. *J Dermatol Treat* 2001; 12: 19–22.
17. Dobson CM, *et al.* Superficial granulomatous pyoderma treated with intravenous immunoglobulin. *J Am Acad Dermatol* 2003; 48: 456–60.
18. Cummins DL, *et al.* Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; 157: 1235–9.
19. Kreuter A, *et al.* Intravenous immunoglobulin for pyoderma gangrenosum. *Br J Dermatol* 2008; 158: 856–7.
20. O'Donnell BP, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; 138: 101–6.
21. Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002; 27: 3–7.
22. Gurmin V, *et al.* Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *Br J Dermatol* 2002; 147: 554–7.
23. Kerr AC, Ferguson J. Type II adult-onset pityriasis rubra pilaris successfully treated with intravenous immunoglobulin. *Br J Dermatol* 2007; 156: 1055–6.
24. Amano H, *et al.* Successful treatment of cutaneous lesions in juvenile dermatomyositis with high-dose intravenous immunoglobulin. *Br J Dermatol* 2007; 156: 1390–2.
25. Goo B, *et al.* Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases. *Br J Dermatol* 2007; 157: 563–8.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2. Intravenous immunoglobulin preparations should be used with caution in patients with renal impairment. Immunoglobulin products containing sucrose may be associated with an increased risk of inducing acute renal failure (see Effects on the Kidneys, below). Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism, and deep-vein thrombosis have been reported after use of intravenous immunoglobulins; these products should be used with caution in obese patients and in patients with pre-existing risk factors for thrombotic events.

Antibody titres for some common pathogens can vary widely not only between products from different manufacturers, but also from lot to lot. Formulations of intravenous immunoglobulins should therefore not be regarded as equivalent.

Reviews.

1. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. *Drug Safety* 1999; 21: 171–85.
2. Wittstock M, *et al.* Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003; 50: 172–5.
3. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; 17: 241–51.
4. Ameratunga R, *et al.* Increased risk of adverse events when changing intravenous immunoglobulin preparations. *Clin Exp Immunol* 2004; 136: 111–13.
5. Singh-Grewal D, *et al.* A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child* 2006; 91: 651–4.
6. Katz U, *et al.* Safety of intravenous immunoglobulin (IVIG) therapy. *Autoimmun Rev* 2007; 6: 257–9.
7. Carbone J. Adverse reactions and pathogen safety of intravenous immunoglobulin. *Curr Drug Safety* 2007; 2: 9–18.
8. Bonilla FA. Intravenous immunoglobulin: adverse reactions and management. *J Allergy Clin Immunol* 2008; 122: 1238–9.

Effects on the blood. Adverse effects on the blood have occasionally been reported after intravenous use of normal immunoglobulin to increase the platelet count in patients with immune thrombocytopenia and in the management of other auto-immune diseases. Reduced platelet adhesiveness with multiple subcutaneous haematomas occurred in one patient.[1] Thrombotic events have occurred after intravenous use,[2-4] particularly in elderly subjects (sometimes fatal) suggesting that a rising platelet count during normal immunoglobulin treatment may represent a risk in patients with severe atherosclerotic disease.[2] However, a review of 34 patients over 60 years of age treated with normal immunoglobulin could not confirm the association.[5]

Haemolytic reactions, including haemolytic disease of the newborn, have sometimes been noted[6-8] and passive transfer of anti-A, anti-B, or anti-D antibodies or active immunisation by blood group substances from normal immunoglobulin preparations has been implicated. It has been suggested[7] that blood phenotyping be carried out before treatment with normal immunoglobulin is started.

Transient neutropenia has occurred after use of normal immunoglobulin in patients with immune thrombocytopenia, but the clinical significance of this effect has been disputed.[9-11]

1. Ljung R, Nilsson IM. High-dose intravenous gammaglobulin: a cautionary note. *Lancet* 1985; i: 467.
2. Woodruff RK, *et al.* Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; ii: 217–18.
3. Go RS, Call TG. Deep venous thrombosis of the arm after intravenous immunoglobulin infusion: case report and literature review of intravenous immunoglobulin-related thrombotic complications. *Mayo Clin Proc* 2000; 75: 83–5.
4. Marie I, *et al.* Intravenous immunoglobulin-associated arterial and venous thrombosis: report of a series and review of the literature. *Br J Dermatol* 2006; 155: 714–21.
5. Prame WD, Crawford RJ. Thrombotic events after intravenous immunoglobulin. *Lancet* 1986; ii: 468.
6. Potter M, *et al.* ABO alloimmunisation after intravenous immunoglobulin infusion. *Lancet* 1988; i: 932–3.
7. Nicholls MD, *et al.* Haemolysis induced by intravenously-administered immunoglobulin. *Med J Aust* 1989; 150: 404–6.
8. Gordon DJ, *et al.* A pediatric case series of acute hemolysis after administration of intravenous immunoglobulin. *Am J Hematol* 2009; 84: 771–2.
9. Majer RV, Green PJ. Neutropenia caused by intravenous immunoglobulin. *BMJ* 1988; 296: 1262.
10. Veys PA, *et al.* Neutropenia following intravenous immunoglobulin. *BMJ* 1988; 296: 1800.
11. Ben-Chetrit E, Putterman C. Transient neutropenia induced by intravenous immune globulin. *N Engl J Med* 1992; 326: 270–1.

Effects on the kidneys. There have been case reports of renal failure or impairment associated with the use of intravenous normal immunoglobulin.[1-3] The incidence of renal failure appears to be greatest with immunoglobulin products containing sucrose.[1,4] The FDA in the USA had issued a warning alerting physicians to the potential risks of acute renal failure associated with intravenous use of normal immunoglobulin products, particularly those containing sucrose.[5]

1. Orbach H *et al.* Intravenous immunoglobulin and the kidney—a two-edged sword. *Semin Arthritis Rheum* 2004; 34: 593–601.
2. Itkin YM, Trujillo TC. Intravenous immunoglobulin-associated acute renal failure: case series and literature review. *Pharmacotherapy* 2005; 25: 886–92.
3. Shah S, Vervan M. Use of i.v. immune globulin and occurrence of associated acute renal failure and thrombosis. *Am J Health-Syst Pharm* 2005; 62: 720–5.
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.
5. FDA. Important drug warning: potential risk of acute renal failure reported to be associated with administration of immune globulin intravenous (human) (Issued 24 September 1999). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105901.htm (accessed 27/08/10)

Effects on the nervous system. Aseptic meningitis has been reported after intravenous use of normal immunoglobulin.[1-5]

Migraine, associated with intravenous immunoglobulin therapy in a patient on 2 occasions, did not recur after prophylaxis with propranolol was started.[6]

Hemiplegia has been reported in a 4-year-old child given intravenous immunoglobulin for immune thrombocytopenic purpura.[7]

1. Kato E, *et al.* Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988; 259: 3269–71.
2. Casteels-Van Daele M, *et al.* Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990; 323: 614–15.
3. Sekul EA, *et al.* Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; 121: 259–62.
4. Picton P, Chisholm M. Aseptic meningitis associated with high dose immunoglobulin: case report. *BMJ* 1997; 315: 1203–4.
5. Boyce TG, Spearman P. Acute aseptic meningitis secondary to intravenous immunoglobulin in a patient with Kawasaki syndrome. *Pediatr Infect Dis J* 1998; 17: 1054–6.
6. Constantinescu CS, *et al.* Recurrent migraine and intravenous immune globulin therapy. *N Engl J Med* 1993; 329: 583–4.
7. Tsiouris J, Tsiouris N. Hemiplegia as a complication of treatment of childhood immune thrombocytopenic purpura with intravenously administered immunoglobulin. *J Pediatr* 1998; 133: 717.

Effects on the skin. Diffuse alopecia has been reported[1] in 3 women within 1 to 4 weeks of treatment with intravenous normal immunoglobulin. There have been reports[2,3] of severe and extensive eczema in elderly patients up to 3 weeks after receiving normal immunoglobulin intravenously. There has also been a report of cutaneous vasculitic rash on the face of a woman receiving intravenous normal immunoglobulin.[4] Severe cutaneous vasculitis has been reported in a patient who received intravenous normal immunoglobulin for type II mixed cryoglobulinaemia.[5] An erythematous eruption occurred on the hands and feet of a patient 3 days after completing a 5-day treatment course of normal immunoglobulin for chronic inflammatory demyelinating polyneuropathy;[6] the lesions resolved 2 to 3 weeks after completion of therapy. A similar eruption had occurred following normal immunoglobulin therapy in 5 previous occasions. Vesiculobullous eruptions have been seen in a patient being treated with intravenous normal immunoglobulin for Stevens-Johnson syndrome.[7]

For mention of a patient with AIDS who developed erythema characteristic of fifth disease following intravenous normal immunoglobulin, see Infection, p. 2408.1.

1. Chan-Lam D, *et al.* Alopecia after immunoglobulin infusion. *Lancet* 1987; i: 1436.
2. Baruchs C, McMillan JC. Eczema after intravenous infusion of immunoglobulin. *BMJ* 1987; 295: 1141.
3. Whittam LR, *et al.* Eczematous reactions to human immune globulin. *Br J Dermatol* 1997; 137: 481–2.
4. Howse M, *et al.* Facial vasculitic rash associated with intravenous immunoglobulin. *BMJ* 1998; 317: 1291.
5. Yebra M, *et al.* Severe cutaneous vasculitis following intravenous infusion of gammaglobulin in a patient with type II mixed cryoglobulinemia. *Clin Exp Rheumatol* 2002; 20: 225–7.
6. Mutasim DF, Sheth PB. An eruption secondary to intravenous immunoglobulin therapy. *Cutis* 2002 69: 35–6, 38.
7. Lin WL, *et al.* Intravenous immunoglobulin-induced, non-eczematous, vesiculobullous eruptions in Stevens-Johnson syndrome. *Am J Clin Dermatol* 2009; 10: 339–42.

Hypersensitivity. Hypersensitivity reactions may occasionally occur after intramuscular or intravenous use of normal immunoglobulins particularly in hypogammaglobulinaemic or agammaglobulinaemic patients. Both immediate and late[1] reactions have occurred.

The IgA content of normal immunoglobulins can result in the development of IgE and IgG anti-IgA antibodies in immunodeficient patients with IgA deficiency. It has been suggested by some[2] that the IgE anti-IgA antibodies are responsible for anaphylaxis although others have disagreed.[3] Two patients who had reactions to conventional normal immunoglobulin preparations tolerated preparations with a low content of IgA.[2] Some manufacturers of normal immunoglobulin preparations recommend that they should not be used in patients with selective IgA deficiencies who have known antibody against IgA.

The IgE content of some preparations has also been suggested as a cause of hypersensitivity reactions[4] although this has been disputed.[5] Complement-activating IgG aggregates may also be involved although the anticomplementary activity of the products does not appear to be related to the incidence of adverse effects.[5]

1. Hachimi-Idrissi S, *et al.* Type III allergic reaction after infusion of immunoglobulins. *Lancet* 1990; 336: 55.
2. Burks AW, *et al.* Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. *N Engl J Med* 1986; 314: 560–4.

3. Hammarström L, Smith CIE. Anaphylaxis after administration of gamma globulin for hypogammaglobulinemia. *N Engl J Med* 1986; 315: 519.
4. Tovo P-A, *et al.* IgE content of commercial intravenous IgG preparations. *Lancet* 1984; i: 458.
5. Newland AC, *et al.* IgE in intravenous IgG. *Lancet* 1984; i: 1406–7.

Infection. An association between use of certain intravenous immunoglobulin preparations and hepatitis C infections led to changes in manufacturing procedures and withdrawal of the affected products from the market.[1-3]

In addition, there has been a report[4] of a patient with AIDS who developed fifth disease (erythema infectiosum) after intravenous normal immunoglobulin treatment for infection with parvovirus. Paradoxically, there has also been a report[5] of life-threatening parvovirus B19 infection, resulting in pure red cell aplasia and aggravation of hepatitis and fulminant disease, from the use of normal immunoglobulin to treat a patient with existing hepatic dysfunction caused by coxsackie B4 virus infection.

1. Quinti I, *et al.* Intravenous gammaglobulin may still infect patients. *BMJ* 1994; 308: 856.
2. Bader J-M. HCV and Gammagard in France. *Lancet* 1994; 343: 1628. Corrections. *ibid.*; 344: 201 and 206.
3. Anonymous. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993–June 1994. *JAMA* 1994; 272: 424–5.
4. French AL, *et al.* Fifth disease after immunoglobulin administration in an AIDS patient with parvovirus-induced red cell aplasia. *Am J Med* 1996; 101: 108–9.
5. Hayakawa F, *et al.* Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* 2002; 118: 1187–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies normal 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

Normal immunoglobulin may interfere with the immune response to live viral vaccines. Such vaccines should therefore be given at least 3 weeks before, or 3 months after, normal immunoglobulin. This does not apply to yellow fever vaccine for immunoglobulins prepared in the UK, nor for booster doses of oral poliomyelitis vaccines. Where such an interval is impractical for immunisation preceding foreign travel it may have to be ignored.

Poliomyelitis vaccine. For a study indicating that normal immunoglobulin has no effect on the antibody response to oral poliomyelitis vaccine, see p. 2412.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Beriglobina; Citax F; Endobulin; Flebogamma; Gammaglobulina; Isiven; Kiovig; Pentaglobin; Sandoglobulina; Seroglubin; Vigam; *Austral.*: Intragam; Octagam; Sandoglobulin†; *Austria*: Beriglobin; Endobulin†; Gammagard; Gammanorm; Gamunex; Ig Vena; Intraglobin†; Intratect; Kiovig; Octagam; Pentaglobin; Privigen; Sandoglobulin†; Subcuvia; Vivaglobin; *Belg.*: Gammagard SD; Gammanorm; Hizentra; Kiovig; Multigam; Nanogam; Octagam; Privigen; Sandoglobuline; Subcuvia; Vivaglobin; *Braz.*: Armoglobulina†; Beriglobina; Endobulin; Gama-Venina†; Octagam; Sandoglobulina; Venimmuna†; *Canad.*: Gamastan; Gammagard; Gamunex; Hizentra; Privigen; Sandoglobulin†; Vivaglobin; *Chile*: Beriglobina P†; Flebogamma; Ig Vena N; Pentaglobin; *China*: Bo Xin (博欣); Chang Sheng Xun Kang (长生迅抗); Gama Laishi (伽玛莱士); *Cz.*: Endobulin†; Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gamunex; Igamplia; Kiovig; Octagam; Pentaglobin†; Privigen; Subcuvia; Venimmun N†; Vivaglobin†; *Denm.*: Beriglobin; Endobulin†; Gammanorm; Gamunex; Hizentra; Kiovig; Octagam; Privigen; Subcuvia; Vivaglobin; *Fin.*: Gammagard; Gammanorm; Gamunex; Nanogam; Octagam; Subcuvia; Vivaglobin†; *Fr.*: Clairyg; Gammagard; Gammanorm; Hizentra; Kiovig; Octagam; Privigen; Sandoglobuline; Subcuvia; Tegeline; Vivaglobin; *Ger.*: Beriglobin; Endobulin†; Flebogamma†; Flebogammadif; Gammagard; Gammanorm; Gamunex; Hizentra; Ig Vena; Intratect; Kiovig; Octagam; Pentaglobin; Privigen; Sandoglobulin†; Subcuvia; Vivaglobin†; *Gr.*: Anosoglobin; Beriglobin; Flebogamma; Gamimune; Gaminex; Gamma-Venin; Gammagard; Globuman; Ig Vena; Intraglobin F; Intratect; Kiovig; Octagam; Omr-IgG; Pentaglobin; Privigen; Sandoglobulin; Subcuvia; Vivaglobin; *Hong Kong*: Baygam†; Flebogamma†; Gamimune N†; Gammagard; Intragam P; Intraglobin F; Kiovig; Octagam†; Pentaglobin; *Hung.*: Gammagard†; Gammanorm; Humaglobin; Intratect; Octagam; Pentaglobin; Vivaglobin; *India*: Bharglob; Cytotect; Flebogamma; Gama-Glob; Gamafine; Gamaglobin; Gamma-IV; Histoglob; Immunorel; IV-Globulin; Iviglob; Norglobin; Octagam; *Indon.*: Gamimune N†; Gammaraas; Gamunex; *Irl.*: Flebogamma; Flebogammadif; Gammagard; Gammanorm; Hizentra; Intraglobin†; Intratect; Kiovig; Nanogam; Privigen; Subcuvia; *Israel*: Beriglobin P; Flebogamma; Gammagard; Gammaplex; Gamunex; Intraglobin F; Intratect; Kiovig; Octagam; Omr-IgG; Privigen; Sandoglobulin; Venoglobulin; Vigam; *Ital.*: Endobulin; Flebogamma; Gammagard; Ig Vena; Intraglobin†; Intratect; Keyven; Kiovig; Octanorm; Pentaglobin; Sandoglobulina; Subcuvia; Venital; Vivaglobin; *Jpn*: Venilon†; Venoglobulin; *Malaysia*: Flebogamma; Gamma-Globulin; IV-Globulin; Vigam; *Mex.*: Beriglobina P; Gamma-Venin P†; Octagam; Pentaglobin; Sandoglobulina; Vigam; *Neth.*: Flebogamma; Gammagard; Gammanorm; GammaQuin; Gamunex; Hizentra; Intratect; Kiovig; Nanogam; Octagam; Privigen; Subcuvia; Vivaglobin†; *Norw.*: Gammanorm; Hizentra; Kiovig; Octagam; Privigen; Subcuvia†; *NZ*: Flebogamma; Gammanorm; Intragam; Octagam; Privigen; Sandoglobulin; *Philipp.*: Gamimune N; Gammagard; IV-Globulin S; Vizcarra; *Pol.*: Endobulin; Gamma-Globulina†; Gammagard; Intraglobin P; Intratect; Kiovig; Pentaglobin; Privigen; Sandoglobulin; Subcuvia; Venimmun; Vivaglobin; *Port.*: Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gamunex; Ig Vena; Kiovig; Octagam; Privigen; Sandoglobulina; Subcuvia; Tegeline; Vivaglobin; *Rus.*: Flebogamma (Флебогамма); Gabriglobine (Габриглобин); Gamimune N (Гамимун Н); Gamunex (Гамунекс); Humaglobin (Хумаглобин); Immunovenin (Иммуновенин); Intraglobin (Интраглобин); Intratect (Интратект); Octagam (Октагам); Pentaglobin (Пентаглобин); *S.Afr.*: Beriglobin; Intragam; Intraglobin F†; Pentaglobin†; Polygam; *Singapore*: Flebogamma; Gammagard; Intragam; Intraglobin F; Octagam†; Pentaglobin; Venoglobulin; Vigam; *Spain*: Beriglobina P; Endobulin†; Flebogamma; Gammagard; Gammaglobulina†; Hizentra; Igamplia; Intratect; Kiovig; Octagamocta; Privigen; Vivaglobin†; *Swed.*: Beriglobin; Flebogamma; Gammagard; Gammanorm; Gamunex; Hizentra; Kiovig; Octagam; Privigen; Subcuvia; Vivaglobin†; Xepol†; *Switz.*: Beriglobin; Endobulin†; Gammanorm; Gamunex; Hizentra; Ig Vena; Intratect; Kiovig; Octagam; Privigen; Redimune; Subcuvia; Vivaglobin; *Thai.*: Flebogamma; Gammagard†; Gammaraas; Ig Vena; Intraglobin†; Kiovig; LIV-Gamma; Octagam; Pentaglobin; Vigam; *Turk.*: Endobulin; Flebogamma; Gamimune N; Gammar; Gamunex; Globuman†; Ig Vena; Intraglobin; Isiven†; Kiovig; Octagam; Pentaglobin; Subcuvia†; Tegeline; Vigam; *UK*: Aragam; Flebogamma; Flebogammadif; Gammagard; Gammanorm; Gammaplex; Gamunex; Hizentra; Intratect; Kiovig; Octagam; Privigen; Sandoglobulin; Subcuvia; Subgam; Vigam; Vivaglobin†; *Ukr.*: Bioven Mono (Биовен Моно); *USA*: Bivigam; Carimune; Flebogamma; Gamastan; Gammagard; Gammaplex; Gamunex†; Hizentra; Octagam; Privigen; Vivaglobin†; *Venez.*: Flebogamma.

Multi-ingredient Preparations. *Arg.*: Histaglobin; *Austria*: Histaglobin†; *India*: Histaglobulin; *Pol.*: Histaglobulina; *Rus.*: Kipferon (Кипферон); *S.Afr.*: Histaglobin†.

Pharmacopoeial Preparations
Ph. Eur.: Human Normal Immunoglobulin for Intravenous Administration; Human Normal Immunoglobulin;
USP 36: Immune Globulin.

Pertussis Immunoglobulins

Inmunoglobulinas contra la tos ferina.
ATC — J06BB13.

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 36: (Pertussis Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with pertussis vaccine. It may contain glycine as a stabilising agent, and a suitable preservative. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Pertussis immunoglobulins have been used for passive immunisation against pertussis (whooping cough) and to prevent or modify pertussis in susceptible persons who have been exposed to infection.

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. *Gr.*: Tosuman; *Turk.*: Tosuman.

Pharmacopoeial Preparations
USP 36: Pertussis Immune Globulin.

Pertussis Vaccines

Vacunas de la tos ferina.
ATC — J07AJ01; J07AJ02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Pertussis Vaccine (Whole Cell, Adsorbed); Vaccinum Pertussis ex Cellulis Integris Adsorbatum). A sterile suspension of inactivated whole cells of one or more strains of *Bordetella pertussis* in saline to which hydrated aluminium phosphate or aluminium hydroxide has been added. It may contain a suitable antimicrobial preservative. The estimated potency is not less than 4 units 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 wP may be used on the label.

Ph. Eur. 8: (Pertussis Vaccine (Acellular, Component, Adsorbed); Vaccinum Pertussis sine Cellulis ex Elementis Praeparatum Adsorbatum). A preparation of individually prepared and purified antigenic components of *Bordetella pertussis* adsorbed on a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It contains either a suitably prepared pertussis toxoid or a pertussis toxin-like protein free from toxic properties produced by expression of a genetically modified form of the corresponding gene. It may also contain filamentous haemagglutinin, pertactin, and other defined antigens such as fimbrial-2 and fimbrial-3 antigens. The final vaccine contains not more than 100 units of bacterial endotoxin per dose. It may contain a suitable antimicrobial preservative. 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 aP may be used on the label.

Ph. Eur. 8: (Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Vaccinum Pertussis Sine Cellulis Copurificatum Adsorbatum). A preparation of antigenic components of *Bordetella pertussis* 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 aP may be used on the label.

Uses and Administration

Pertussis vaccines are used for active immunisation against pertussis (whooping cough) (p. 198.3). Acellular pertussis vaccines have taken the place of whole-cell vaccines in several countries including the UK and the USA.

For primary immunisation combined pertussis vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae vaccines (p. 2385.3) are used. For pre-school boosters diphtheria, tetanus, pertussis, and poliomyelitis vaccines (p. 2385.2) are sometimes given. For discussion of immunisation schedules, see below.

References.
1. Casey JR, Pichichero ME. Acellular pertussis vaccine safety and efficacy in children, adolescents and adults. *Drugs* 2005; 65: 1367–89.
2. WHO. Pertussis vaccines–WHO position paper. *Wkly Epidem Rec* 2005; 80: 31–9. Also available at: http://www.who.int/immunization/topics/wer8004pertussis_Jan_2005.pdf (accessed 10/12/09)
3. Guiso N. Bordetella pertussis and pertussis vaccines. *Clin Infect Dis* 2009; 49: 1565–9.

Immunisation schedules. Pertussis is a common, highly infectious, respiratory disease, mainly affecting children, and for which there is no effective treatment. WHO estimates that 20 to 40 million cases of pertussis occur annually and that the disease is responsible for 200 000 to 400 000 deaths each year. The highest incidence of pertussis occurs in developing countries where immunisation is low.

Combined vaccines are now used in most countries but both the strength of the pertussis component and production methods vary, leading to vaccines of different potencies. The considerably higher cost of acellular over whole-cell pertussis vaccines means that the latter are still used widely in developing countries.

Depending upon the country, the age at which a child is given the first dose of a combined vaccine varies from 5 weeks to 6 months. (For summaries of immunisation schedules in the UK and USA, see under Vaccines, p. 2373.3.) In countries with a high incidence of pertussis, WHO recommends that immunisation should start at 6 weeks of age and that the schedule involve 3 doses at monthly intervals followed by a booster dose at 18 months to 6 years of age. In the UK and USA, booster doses should be given after the end of the primary series of 3 injections before entry to school. Several reports have described the use of a 2-dose widely-spaced primary immunisation schedule and this would indeed simplify procedures in developing countries; however, the limitation of such a schedule is the long period of risk between doses without adequate protection and unless the interval can be shortened to 4 weeks, the wide use of such a schedule is not advisable in endemic areas.

Vaccine development. Dissatisfaction with whole-cell vaccines in the 1970s because of adverse reactions led to reduced uptake and a resurgence of pertussis in several countries. In Japan, research into less reactogenic pertussis vaccines resulted in the introduction of acellular vaccines for routine vaccination in the early 1980s. Acellular pertussis vaccines can contain a variety of pertussis components:

- pertussis toxin (PT; also formerly known as lymphocytosis-promoting factor, LPF)
- filamentous haemagglutinin (FHA)
- pertactin (PRN)
- fimbrial agglutinogens (FIM) 2 and 3

The acellular vaccines commonly used are a 3-component vaccine containing PT/FHA/PRN and a 5-component vaccine containing PT/FHA/PRN/FIM2/FIM3. The vaccine used in combination vaccines for primary immunisation in the UK is the 5-component vaccine. The 3-component vaccine does not provide the same level of protection against whooping cough in primary immunisation. Both 3-component and 5-component vaccines may be used in combination vaccines for pre-school boosting. The combination vaccine used for pre-school boosting that contains 5-component pertussis vaccine does not provide the recommended strength of diphtheria to be used for primary immunisation.

Acellular vaccines are recommended in the UK and USA for both primary immunisation in infants and for the booster doses in young children before school entry. Whole-cell vaccines are still, however, widely used in other countries, particularly in the developing world.

Adverse Effects

As for vaccines in general, p. 2375.1.

Local reactions may occur at the site of injection of pertussis vaccines or pertussis-containing vaccines and use may be followed by fever and irritability. Local reactions and fever occur less frequently with the acellular vaccine than with whole-cell vaccine, especially in children over 6 months of age and adults. However, booster doses of acellular pertussis-containing vaccines are associated with an increased risk of injection site reactions.

Severe reactions which have been reported include persistent screaming and generalised collapse but these effects were generally associated with an earlier type of vaccine and the reactions are rarely seen with the currently available vaccines.

Rare neurological adverse reactions have included convulsions and encephalopathy. There has been much debate, however, on the causal role of pertussis vaccine in such reactions (see below for detailed discussion). It should be remembered that neurological complications occur more frequently as a consequence of pertussis infection than from vaccination.

Asthma. A higher incidence of asthma was reported in 243 children who had received whole-cell pertussis vaccine than in 203 children who had not.[1] However, follow-up of a large Swedish study[2] showed no difference in the incidence of wheezing or allergic reactions between children who had received diphtheria, tetanus, and whole-cell pertussis vaccines and those who had not. A later prospective study[3] also found no evidence that whole-cell pertussis vaccination increased the risk of wheezing illness in young children. Furthermore, no association was found between pertussis vaccination in infancy and development of asthma in children aged up to 7 years in a later study of the same group of children.[4] A population-based cohort study[5] also reported no evidence of an increased risk of wheezing or asthma in more than 6000 children 8 to 12 years after vaccination in infancy with either an acellular or whole-cell pertussis vaccine.

1. Odent MR, *et al.* Pertussis vaccination and asthma: is there a link? *JAMA* 1994; **272:** 592–3.
2. Nilsson L, *et al.* Lack of association between pertussis vaccination and symptoms of asthma and allergy. *JAMA* 1996; **275:** 760.
3. Henderson J, *et al.* Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. *BMJ* 1999; **318:** 1173–6.
4. Maitra A, *et al.* Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* 2004; **328:** 925–6.
5. Spycher BD, *et al.* Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. *Pediatrics* 2009; **123:** 944–50. Correction. *ibid.*; 1437.

Effects on the nervous system. There has been continuing debate over several decades concerning the perceived link between pertussis vaccination and brain damage. Anxiety among both the public and health-care professionals in the UK in the mid-1970s over the safety of whole-cell pertussis vaccines led to a fall in the acceptance rates for infant vaccination and major epidemics of pertussis in 1977/79 and 1981/83. Since that time confidence has been restored and, with the introduction of acellular vaccines, the vast majority of infants now receive the vaccine before their second birthday. Comparison of whole-cell vaccines with acellular vaccines has since confirmed that the latter are associated with a greatly reduced incidence of serious neurological disorders.[1]

The consensus of opinion now seems to be that there is a temporal, but not necessarily causal, relationship between whole-cell pertussis vaccine and acute neurological illness that may occasionally lead to long-term dysfunction, and that risks of not immunising are greater than the potential risks associated with the vaccine.

The difficulty in ascertaining whether a causal relationship exists between whole-cell pertussis vaccine (usually given as diphtheria, tetanus, and pertussis (DTP) vaccine) and acute neurological reactions arises partly because primary vaccination is given at an age when neurological dysfunction with other causes is often first manifested. The temporal relationship seen may be entirely coincidental, may result from indirect factors such as pyrexia after vaccination, or may represent a direct effect of DTP vaccine. Much of the evidence is based on large epidemiological studies,[2-7] in particular the National Childhood Encephalopathy Study (NCES)[8] from the UK and its 10-year follow-up.[9] Serious acute neurological illnesses reported to the NCES[8] were found to be more common in infants immunised within 7 days (relative risk 2.4), and especially within 72 hours of onset, than in unimmunised children. For previously normal children, irrespective of outcome, the risk was estimated as 1 in 110 000 injections. In a subset of cases diagnosed as infantile spasms,[10] no link with vaccination was found overall, but there was a small excess of cases of infantile spasm in previously normal children who had received either DTP or diphtheria and tetanus vaccines during the previous 7 days (relative risk 2.0-2.5) followed by a corresponding deficit during the next 3 weeks. This suggested that vaccination may trigger the onset of spasms in a child with an underlying predisposition.

In 1991, the USA Institute of Medicine reviewed the available data, including the NCES results, and concluded that a causal relationship between the whole-cell pertussis component of DTP vaccine and acute encephalopathy probably existed, with an estimated excess risk of 0 to 10.5 per million vaccinations.[11] They concurred with the conclusion that a causal relationship between vaccination and infantile spasm was unlikely.

The NCES 10-year follow-up found that children who had had a serious acute neurological illness (excluding infantile spasms) had an increased risk of death or long-term dysfunction, but the risk was no greater in children given DTP vaccine in the 7 days before the original acute illness.[9] The National Vaccines Advisory Committee concluded that the results were insufficient to determine whether DTP vaccine influenced the development of chronic neurological dysfunction, and this conclusion has been accepted by both the Advisory Committee on Immunization Practices[12] and the American Academy of Pediatrics.[13]

1. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. *Brain Dev* 2004; **26:** 296–300.
2. Pollock TM, Morris J. A 7-year survey of disorders attributed to vaccination in North West Thames Region. *Lancet* 1983; **i:** 753–7.
3. Pollock TM, *et al.* Symptoms after primary immunisation with DTP and with DT vaccine. *Lancet* 1984; **ii:** 146–9.
4. Walker AM, *et al.* Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatrics* 1988; **81:** 345–9.
5. Shields WD, *et al.* Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr* 1988; **113:** 801–5.
6. Griffin MR, *et al.* Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *JAMA* 1990; **263:** 1641–5.
7. Gale JL, *et al.* Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine: a population-based case-control study. *JAMA* 1994; **271:** 37–41.
8. Miller DL, *et al.* Pertussis immunisation and serious acute neurological illness in children. *BMJ* 1981; **282:** 1595–9.
9. Miller D, *et al.* Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 1993; **307:** 1171–6.
10. Bellman MH, *et al.* Infantile spasms and pertussis immunisation. *Lancet* 1983; **i:** 1031–4.
11. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines: summary of a report of the Institute of Medicine. *JAMA* 1992; **267:** 392–6.
12. CDC. Update: vaccine side effects, adverse reactions, contraindications, and precautions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996; **45** (RR-12): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4512.pdf (accessed 25/05/06)
13. Committee on Infectious Disease, American Academy of Pediatrics. The relationship between pertussis vaccine and central nervous system sequelae: continuing assessment. *Pediatrics* 1996; **97:** 279–81.

Precautions

As for vaccines in general, p. 2375.2. The precautions and contra-indications to the use of pertussis vaccines have sometimes been more stringent than is now considered necessary because of the controversy about their potential adverse effects, especially neurotoxicity (see Effects on the Nervous System, above). In the UK it is now recommended that immunisation should continue with acellular pertussis vaccine even when episodes of fever (irrespective of severity), hypotonic-hyporesponsive episodes, persistent crying or screaming, or severe local reactions (irrespective of extent) have occurred after a preceding dose. Children who have had a local or general reaction to a whole-cell pertussis vaccine should complete their immunisation with acellular pertussis vaccine.

Whether or not children with a personal or family history of convulsions or epilepsy or who have suffered cerebral damage in the neonatal period should receive pertussis vaccines appears to have been the most difficult question to resolve in the past. In the UK it is now considered that a family history of seizures is not a contra-indication to immunisation. When a child has a history of seizures associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal; advice on the prevention of fever should be given at the time of immunisation (see Fever and Hyperthermia, p. 11.3 for comments on the prevention of fever after immunisation). Similarly when there is a history of seizures not associated with fever, but no evidence of neurological deterioration, immunisation should proceed as normal. If a seizure associated with fever occurs within 72 hours of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 24 hours. Immunisation should also be carried out in children with a history of cerebral damage in the neonatal period unless there is evidence of an evolving neurological abnormality. In children with a neurological problem that is still evolving it is recommended that immunisation should be deferred until the condition is stable. If a child develops encephalopathy or encephalitis within 7 days of immunisation, further immunisation should be deferred until the condition is stable if no underlying cause is found and the child has not recovered completely within 7 days.

A personal or family history of hypersensitivity reactions is not generally considered to be a contra-indication to the use of pertussis vaccines, and neither are stable neurological conditions such as spina bifida, congenital brain abnormality, or perinatal hypoxic ischaemic encephalopathy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pertussis 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. *Neth.*: Acellulair†.

Pharmacopoeial Preparations

Ph. Eur.: Pertussis Vaccine (Acellular Component, Adsorbed); Pertussis Vaccine (Acellular, Co-purified, Adsorbed); Pertussis Vaccine (Whole Cell, Adsorbed).

Pigbel Vaccines

Vacuna de Pigbel; Vacunas de la enteritis necrotizante.

Profile

A vaccine against pigbel (necrotising enteritis), a disease occurring mainly in children in the highlands of Papua New Guinea, is used for active immunisation against the disease. The vaccine consists of an adsorbed *Clostridium perfringens* type C toxoid.

An immunisation programme, in which pigbel vaccine was given to children at 2, 4, and 6 months of age and, initially, to older children, was introduced in Papua New Guinea in 1980.[1] A survey found a sustained overall fall in the incidence of severe pigbel in children coincident with the increased induced immunity. However, protection may be relatively short-lived and boosters may be necessary for full protection of young children. A later review[2] conducted to inform vaccination policy, noted that a newer vaccine was available but that the disease continued to be a problem.

1. Lawrence GW, *et al.* Impact of active immunisation against enteritis necrotizans in Papua New Guinea. *Lancet* 1990; **336:** 1165–7.
2. Poka H, Duke T. In search of pigbel: gone or just forgotten in the highlands of Papua New Guinea? *P N G Med J* 2003; **46:** 135–42.

Plague Vaccines

Vacunas de la peste.

ATC — J07AK01.

Uses and Administration

Plague vaccines have been used for active immunisation against plague in those occupationally exposed to the organism and in some field workers in infected areas. They may reduce morbidity and mortality in bubonic plague but their activity against pneumonic plague is unknown.

References.

1. Cornelius C, *et al.* Protective immunity against plague. *Adv Exp Med Biol* 2007; **603:** 415–24.
2. Smiley ST. Current challenges in the development of vaccines for pneumonic plague. *Expert Rev Vaccines* 2008; **7:** 209–21.

3. Smiley ST. Immune defense against pneumonic plague. *Immunol Rev* 2008; 225: 256–71.
4. Alvarez ML, Cardineau GA. Prevention of bubonic and pneumonic plague using plant-derived vaccines. *Biotechnol Adv* 2010; 28: 184–96.
5. Feodorova VA, Corbel MJ. Prospects for new plague vaccines. *Expert Rev Vaccines* 2009; 8: 1721–38.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Interactions

As for vaccines in general, p. 2375.3.

Pneumococcal Vaccines

Vacunas neumocócicas.
ATC — J07AL01; J07AL02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Pneumococcal Polysaccharide Vaccine; Vaccinum Pneumococcale Polysaccharidum). A mixture of purified polysaccharide capsular antigens from 23 differing serotypes of *Streptococcus pneumoniae*. Each 0.5-mL dose contains 25 micrograms of each of the 23 polysaccharide types. An antimicrobial preservative may be added. The vaccine has a pH of 4.5 to 7.4. 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 Pneumo may be used on the label.

Ph. Eur. 8: (Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Vaccinum Pneumococcale Polysaccharidicum Coniugatum Adsorbatum). A sterile suspension of purified capsular polysaccharides obtained from *Streptococcus pneumoniae* serotypes individually conjugated to a carrier protein. The carrier protein used may vary for the various polysaccharide conjugates contained in a multivalent vaccine. The vaccine may be adsorbed on a suitable adjuvant or adsorbant. 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 Pneumo(conj) may be used on the label.

Uses and Administration

Of the many serotypes of *Streptococcus pneumoniae* the 23 from which antigens are obtained for the most commonly available pneumococcal vaccine are considered to cause up to 96% of pneumococcal disease.

Pneumococcal vaccines are used for active immunisation in those at increased risk from infection with the types of *Streptococcus pneumoniae* contained in the vaccine. Pneumococcal vaccines may be in the form of an unconjugated 23-valent polysaccharide vaccine (PPV; suitable only for patients over 2 years of age) or as a conjugate vaccine (PCV) containing 7 serotypes (suitable for infants aged 2 months to 5 years). A conjugated vaccine containing 13 serotypes (PCV-13), suitable for infants and children aged 6 weeks to 17 years of age, has been approved for use in some countries and has replaced the vaccine containing 7 serotypes in routine childhood immunisation programmes. The PCV-13 vaccine may also be used in adults aged 50 years and older.

In the UK, it is recommended that immunisation should be part of the routine childhood immunisation programme and considered in all persons for whom pneumococcal infection is likely to be more common and/or serious, such as those aged 65 years and over and those aged two months and over in clinical risk groups. At-risk groups are considered to be:

- those who have undergone splenectomy and those with splenic dysfunction, including that due to sickle-cell anaemia and coeliac disease
- patients with immunodeficiency or immunosuppression due to disease or treatment, including HIV infection at all stages
- persons with chronic cardiac, pulmonary, hepatic, or renal impairment, including nephrotic syndrome, or diabetes mellitus
- persons with CSF shunts
- persons with cochlear implants

An antibody response develops by the third week, and usually lasts about 5 years. The antibody response is less reliable and declines more rapidly in young children and persons with impaired immune function.

A single dose of 0.5 mL of the 23-valent vaccine, containing 25 micrograms of each of the 23 polysaccharide types, is given to at-risk adults and children over 2 years of age by intramuscular injection (or subcutaneously if there are bleeding disorders). Previously unvaccinated children and adults undergoing elective splenectomy, chemotherapy, or other immunosuppressive treatment are at increased risk of pneumococcal disease and should be vaccinated accordingly (see below). The vaccine should be given at least 2 weeks (but preferably 4 to 6 weeks) before treatment. Revaccination is not generally recommended except, after 5 years, in patients likely to have rapidly declining antibody concentrations (for example, those with asplenia or splenic dysfunction and those with nephrotic syndrome).

The 7- and 13-valent pneumococcal conjugate vaccines are given by intramuscular injection. In the UK, the 13-valent PCV is suitable for infants and children from 6 weeks of age and is recommended as part of the routine immunisation schedule; doses of 0.5 mL are given at 2 and 4 months and a reinforcing dose is given at 13 months of age. A single dose of a 23-valent PPV is given to all adults 65 years and over. Additional recommendations are included in the vaccination schedule for the clinical risk groups above:

- *children 2 to 12 months of age (including those with asplenia, splenic dysfunction, or who are immunocompromised)*: vaccinate with a 13-valent PCV according to the routine immunisation schedule, followed by a single dose of a 23-valent PPV after their second birthday
- *children, aged 12 months to under 5 years*: give one dose of a 13-valent PCV, followed by a single dose of a 23-valent PPV after their second birthday (and at least 2 months after the dose of PCV)
  for those in the above group with asplenia, splenic dysfunction, or who are immunocompromised: give 2 doses of a 13-valent PCV, at least 2 months apart, followed by a single dose of a 23-valent PPV after their second birthday (and at least 2 months after the final dose of PCV)
- *from 5 years of age*: a single dose of a 23-valent PPV

In the USA, the 13-valent PCV is recommended for infants and children from 2 to 59 months of age as part of the primary immunisation schedule and for children aged 60 to 71 months of age with underlying medical conditions. Three doses are recommended as part of the routine primary immunisation schedule at 2, 4, and 6 months of age and a reinforcing dose is given at 12 to 15 months of age. A supplementary dose of the 13-valent PCV should be given to high-risk groups through to 71 months who have previously completed vaccination with 7-valent PCV. A dose of the 23-valent PPV should also be given to high-risk groups at 2 years of age (or as soon as possible after a high-risk chronic illness is diagnosed in those older than 2 years) and at least 2 months after the final dose of 13-valent PCV. A second dose of 23-valent PPV is recommended 5 years after the first dose in those with sickle-cell disease, asplenia, splenic dysfunction, HIV-infection, or who are immunocompromised.

Guidelines and recommendations.

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2. WHO. 23-valent pneumococcal polysaccharide vaccine: WHO position paper. *Wkly Epidem Rec* 2008; 83: 373–84. Also available at: http://www.who.int/wer/2008/wer8342.pdf (accessed 05/03/13)
3. American Academy of Pediatrics, Committee on Infectious Diseases. Policy Statement—Recommendations for the prevention of *Streptococcus pneumoniae* infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics* 2010; 126: 186–90. Also available at: http://pediatrics.aappublications.org/cgi/reprint/126/1/186 (accessed 05/03/13)
4. CDC. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59: 1–18. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf (accessed 05/03/13)
5. CDC. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR* 2010; 59: 1102–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm (accessed 05/03/13)
6. CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2012; 61: 816–19. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm (accessed 05/03/13)
7. WHO. Pneumococcal vaccines WHO position paper - 2012 - recommendations. *Vaccine* 2012; 30: 4717–18. Also available at: http://www.who.int/wer/2012/wer8714.pdf (accessed 05/03/13)

Reviews and references.

1. Sheikh A, *et al.* Pneumococcal vaccine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 22/04/05).
2. Davies EG, *et al.* Pneumococcal vaccines for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/04/06).
3. Lin PL, *et al.* Safety and immunogenicity of the American Academy of Pediatrics-recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics* 2005; 116: 160–7.
4. Bernatoniene J, Finn A. Advances in pneumococcal vaccines: advantages for infants and children. *Drugs* 2005; 65: 229–55.
5. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. *Clin Infect Dis* 2008; 47: 1328–38.
6. Adamkiewicz TV, *et al.* Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics* 2008; 121: 562–9.
7. Jansen AGSC, *et al.* Pneumococcal conjugate vaccines for preventing otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 11/12/09).
8. Chang CC, *et al.* Pneumococcal vaccines for children and adults with bronchiectasis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 11/12/09).
9. Goldblatt D, *et al.* The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50-80 years. *Clin Infect Dis* 2009; 49: 1318–25.
10. Bryant KA, *et al.* Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010; 125: 866–75. Also available at: http://pediatrics.aappublications.org/cgi/reprint/125/5/866 (accessed 29/07/10)
11. Duggan ST. Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed) [Prevenar 13]. *Drugs* 2010; 70: 1973–86.
12. Sucher AJ, *et al.* Prevnar 13, the new 13-valent pneumococcal conjugate vaccine. *Ann Pharmacother* 2011; 45: 1516–24.
13. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. *Clin Infect Dis* 2011; 52: 1241–7.
14. Sanford M. Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed): in older adults. *Drugs* 2012; 72: 1243–55.
15. Moberley S, *et al.* Vaccines for preventing pneumococcal infection in adults. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2013 (accessed 05/03/13).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1. Unless otherwise stated, the information below refers to the unconjugated polyvalent vaccine.

Revaccination of adults is not routinely recommended because of the increased incidence and severity of adverse reactions.

Pneumococcal vaccination is relatively ineffective in patients with multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, especially during treatment, and in chronic alcoholism. In patients with Hodgkin's disease the use of pneumococcal vaccines is not recommended in those who have received extensive chemotherapy or nodal irradiation. Pneumococcal vaccines should be given at least 2 weeks (and preferably 4 to 6 weeks) before starting immunosuppressive therapy or be delayed until at least 3 months after completion of therapy.

A satisfactory response to the unconjugated polyvalent pneumococcal vaccines is not obtained in children less than 2 years of age and therefore immunisation of this age group with this vaccine is not recommended. However, a pneumococcal conjugate vaccine is available that may be given to infants from 2 months of age.

Effects on the blood. Relapses have occurred on rare occasions in patients with stabilised immune thrombocytopenia at 2 to 14 days after vaccination against pneumococcal infections, lasting for up to 2 weeks. One such case was reported[1] following revaccination less than 2.5 years after an uneventful primary vaccination with pneumococcal vaccine.

1. Neil VS. Long term management after splenectomy: revaccination may cause relapse. *BMJ* 1994; 308: 339.

Effects on the kidneys. Glomerulonephritis was described[1] in a splenectomised patient after use of pneumococcal vaccine. It was postulated that high antibody titres from a recent pneumococcal infection could have contributed. Minimal change nephrotic syndrome with mild interstitial nephritis following pneumococcal vaccination was suggested as the cause of oedema of the face and legs, visual disturbance suggestive of uveitis, and massive proteinuria in a 67-year-old woman who had been vaccinated about 4 months earlier.[2]

1. Tan SY, Cumming AD. Vaccine related glomerulonephritis. *BMJ* 1993; 306: 248.
2. Kikuchi Y, *et al.* Minimal change nephrotic syndrome, lymphadenopathy and hyperimmunoglobulinemia after immunization with a pneumococcal vaccine. *Clin Nephrol* 2002; 58: 68–72.

Effect of nutritional status. An impaired antibody response to pneumococcal vaccine was reported[1] in elderly patients with low serum concentrations of vitamin B_{12}.

1. Fata FT, *et al.* Impaired antibody responses to pneumococcal polysaccharide in elderly patients with low serum vitamin B12 levels. *Ann Intern Med* 1996; 124: 299–304.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pneumococcal vaccine (unconjugated) 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.*: Pneumo 23; Pneumovax 23; Prevenar; Prote-Neu; Synflorix; *Austral.*: Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *Austria*: Pneumo 23; Prevenar 13; Prevenar; Synflorix; *Belg.*: Pneumo 23; Prevenar; Synflorix; *Braz.*: Vacina Pneumococica Conjugada 7-Valente; Vaci-

na Pneumococica Polivalente; *Canad.*: Pneumo 23; Pneumovax 23; Prevnar 13; Prevnar; Synflorix; *Chile*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *China*: Hui Yi Kang (惠益康); Pneumo 23 (优博 23); Pneumovax (细其法); Prevenar (沛儿); *Cz.*: Pneumo 23; Prevenar; Synflorix; *Denm.*: Pneumovax; Prevenar; *Fin.*: Pneumovax; Prevenar; *Fr.*: Pneumo 23; Pneumovax†; Prevenar 13; Prevenar†; *Ger.*: Pneumovax 23; Prevenar; Synflorix; *Gr.*: Pneumo 23; Pneumovax 23; Pnu-Imune 23; Prevenar; Synflorix; *Hong Kong*: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; *Hung.*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; *Indon.*: Pneumo 23; Prevenar; Synflorix; *Irl.*: Pneumovax II; Prevenar; Synflorix; *Israel*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *Ital.*: Pneumo 23†; Pneumovax; Prevenar; *Malaysia*: Pneumo 23; Prevenar; Synflorix; *Mex.*: Prevenar; Pulmovax; *Neth.*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *Norw.*: Pneumovax; Prevenar 13; Prevenar†; Synflorix†; *NZ*: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; *Philipp.*: Pneumo 23; Pneumovax; Prevenar; *Pol.*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *Port.*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar; Synflorix; *Rus.*: Prevenar (Превенар); *S.Afr.*: Imovax Pneumo 23; Pneumovax 23; Prevenar; *Singapore*: Pneumo 23; Pneumovax 23; Prevenar 13; Prevenar†; Synflorix; *Spain*: Pneumo 23; Pneumovax 23; Prevenar; Synflorix; *Swed.*: Pneumo 23†; Pneumovax; Prevenar 13; Prevenar; Synflorix; *Switz.*: Pneumovax 23; Prevenar 13; Prevenar†; *Thal.*: Pneumo 23; Pneumovax 23; Prevnar 13; Prevnar†; Synflorix; *Turk.*: Pneumo 23; Prevenar; Synflorix; *UK*: Pneumovax II; Prevenar; Synflorix; *Ukr.*: Prevenar 13 (Превенар 13); Synflorix (Синфлорикс); *USA*: Pneumovax 23; Prevnar; *Venez.*: Prevenar.

Pharmacopoeial Preparations

Ph. Eur.: Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed); Pneumococcal Polysaccharide Vaccine.

Poliomyelitis Vaccines

Polio Vaccines; Poliovirus Vaccines; Vacunas de la polio; Vacunas de la poliomielitis.

ATC — J07BF01; J07BF02; J07BF03; J07BF04.

NOTE. Inactivated poliomyelitis vaccines are sometimes termed Salk Vaccine and live (oral) poliomyelitis vaccines are sometimes termed Sabin Vaccine.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Poliomyelitis Vaccine (Inactivated); Vaccinum Poliomyelitidis Inactivatum). A liquid preparation of suitable strains of poliomyelitis virus, types 1, 2, and 3, grown in suitable cell cultures and inactivated by a suitable method. Permitted antibacterials may be used in its production and it may contain preservatives. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that IPV may be used on the label.

Ph. Eur. 8: (Poliomyelitis Vaccine (Oral); Vaccinum Poliomyelitidis Perorale; Poliomyelitis Vaccine, Live (Oral) BP 2014). A liquid preparation of suitable live attenuated strains of poliomyelitis virus, types 1, 2, or 3, grown in suitable, approved cell cultures; it may contain any one of the 3 virus types or combinations of them. The trivalent vaccine is standardised for virus titre which is not less than 6.0 log $CCID_{50}$ for type 1, not less than 5.0 log $CCID_{50}$ for type 2, and not less than 5.5 log $CCID_{50}$ for type 3 per dose. Permitted antibacterials may be used in its production. 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 OPV may be used on the label.

Uses and Administration

Poliomyelitis vaccines are used for active immunisation against poliomyelitis. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. There are 3 serotypes of poliovirus, and both live trivalent (oral) and inactivated trivalent poliomyelitis vaccines are used in routine immunisation programmes. Monovalent oral poliomyelitis vaccines against either wild poliovirus types 1 or 3 are used during supplementary immunisation activities in the highest-risk areas; an oral bivalent poliomyelitis vaccine is also being tried. The oral vaccine stimulates the formation of antibodies both in the blood and in the mucosal tissues of the gastrointestinal tract.

In the UK, a trivalent inactivated poliomyelitis vaccine is recommended for the primary immunisation of all age groups, given as a course of 3 doses at intervals of 4 weeks. It is given intramuscularly as a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine. For children who received primary immunisation during infancy, reinforcing doses are recommended at school entry (diphtheria, tetanus, pertussis, and poliomyelitis) and before leaving school (diphtheria, tetanus, and poliomyelitis). Further reinforcing doses are necessary only in adults exposed to infection including travellers to countries where poliomyelitis is epidemic or endemic and healthcare workers in contact with poliomyelitis cases. A single dose is given, repeated every 10 years if necessary.

In the USA, the recommended schedule consists of four doses of inactivated vaccine given at 2 months, 4 months, 6 to 18 months, and 4 to 6 years of age.

On the occurrence of a single case of paralytic poliomyelitis from wild virus, a single dose of the oral vaccine is recommended for all persons in the neighbourhood, regardless of whether they have previously been immunised. A primary course should be completed in previously unimmunised individuals.

References.

1. CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR* 2009; 58: 829–30. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5830a3.htm (accessed 30/06/10)
2. WHO. Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. *Wkly Epidem Rec* 2010; 85: 213–28. Also available at: http://www.who.int/wer/2010/wer8523.pdf (accessed 30/06/10)

Choice of vaccine. Two types of poliomyelitis vaccine are available: live attenuated oral poliomyelitis vaccine (OPV) and inactivated (killed) poliomyelitis vaccine (IPV) given by injection. Both vaccines are highly effective against all 3 types of poliovirus but there are advantages and disadvantages associated with their use.

The *advantages* of OPV are:

- it produces an immune response in both the blood and in the lining of the gut, thus preventing both spread of infection to the CNS and multiplication of the virus in the gastrointestinal tract and hence transmission via the stools and saliva
- it is given orally and is therefore easy to give without specialist training
- it is relatively inexpensive, an important consideration in developing countries in particular.

The *disadvantage* of OPV is:

- it causes very rare cases of vaccine-associated paralytic poliomyelitis (VAPP).

The *advantage* of IPV is:

- it is not a live vaccine and as such carries no risk of VAPP.

The *disadvantages* of IPV are:

- it confers very little immunity in the gastrointestinal tract, hence when an individual immunised with IPV is infected with wild poliovirus the virus can still multiply in the intestines and be shed in the stools, thus risking continued transmission
- trained health workers are required to give it by injection
- it costs far more than OPV.

Poliomyelitis has now been eradicated from most countries in the world (see below) and hence many, including the UK and the USA, consider it appropriate to use IPV exclusively for routine immunisation. However, the Global Polio Eradication Initiative will continue to use OPV where necessary until global eradication is achieved, at which time it has stated that the use of OPV should cease as soon as possible while population immunity against poliomyelitis and surveillance sensitivity for paralysis remain high, and be replaced by routine use of IPV.[1]

1. WHO. Framework for national policy makers in OPV-using countries: cessation of routine oral polio vaccine (OPV) use after global polio eradication. Geneva: WHO, 2005. Also available at: http://www.polioeradication.org/content/publications/OPVCessationFrameworkEnglish.pdf (accessed 12/10/05)

Eradication of infection. By the mid-1980s poliomyelitis was declining in many regions of the world due to mass oral poliomyelitis vaccine immunisation activities and in 1988, WHO announced the goal of eradicating poliomyelitis by the year 2000. Other bodies joined the project which became known as the Global Polio Eradication Initiative.[1] Although the goal was not achieved in 2000, very considerable progress has been made. In 1988, wild poliovirus (WPV) was endemic in 125 countries and more than 1000 children became paralysed every day. The last cases of WPV type 2 were reported in October 1999[2] and by 2006 indigenous transmission of WPV2 infection had been interrupted globally;[3] by 2008 transmission of indigenous WPV types 1 and 3 (WPV1 and WPV3) still occurred in 4 countries (Afghanistan, India, Nigeria, and Pakistan).[2-4] These countries remain a source of WPV that may be reintroduced into countries where transmission had previously stopped; in 2009, 207 cases were reported from 15 countries after WPV importation.[2]

Once global WPV transmission has been interrupted, the greatest risk of poliomyelitis being reintroduced will be from the attenuated viruses contained in oral poliomyelitis vaccine, which in rare cases can result in vaccine-associated paralytic polio (VAPP) and outbreaks due to vaccine-derived polioviruses (VDPV).[1] The first report of circulating VDPV occurred in 2000 and in 2009 VDPVs were detected in 6 countries;[2] VDPVs can circulate even in well-immunised communities and produce polio outbreaks in areas with low rates of oral polio vaccine coverage. Furthermore, they can replicate for years in immunocompromised persons.[4] This led to the realisation that complete eradication of poliomyelitis must eventually also include the eradication of the live oral vaccine and that a high level of universal immunity against poliomyelitis will need to be maintained, with the current inactivated poliomyelitis vaccine or a new generation inactivated poliomyelitis vaccine, even after wild poliovirus is eradicated.[5]

1. Global Polio Eradication Initiative. Information available at: http://www.polioeradication.org (accessed 14/12/09)
2. CDC. Progress towards interruption of wild poliovirus transmission—worldwide, 2009. *MMWR* 2010; 59: 545–50. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5918a1.htm (accessed 30/06/10)
3. CDC. Wild poliovirus type 1 and type 3 importations—15 countries, Africa, 2008–2009. *MMWR* 2009; 58: 357–62. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5814a1.htm (accessed 14/12/09)
4. CDC. Update on vaccine-derived polioviruses—worldwide, January 2008–June 2009. *MMWR* 2009; 58: 1002–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5836a3.htm (accessed 14/12/09)
5. Chumakov K, Ehrenfeld E. New generation of inactivated poliovirus vaccines for universal immunization after eradication of poliomyelitis. *Clin Infect Dis* 2008; 47: 1587–92.

Adverse Effects

As for vaccines in general, p. 2375.1.

Vaccine-associated paralytic poliomyelitis has been reported rarely in recipients of oral poliomyelitis vaccines and in contacts of recipients (see p. 2412.1).

Carcinogenicity. Some poliomyelitis vaccines given in the 1950s and 1960s were found to be contaminated with Simian virus (SV40) from the monkey cell cultures used in the manufacturing process.[1] Once the contamination was realised, steps were taken to eliminate it from future vaccines. However, SV40 is believed to possess biological properties consistent with cancer-causing viruses and epidemiological studies have consequently been conducted to assess whether vaccine recipients have subsequently developed cancer. Although these studies did not find any increased cancer risk, a report by the USA Institute of Medicine in 2002 concluded that these studies were sufficiently flawed to preclude any conclusion being reached. Studies have also assessed the risk to offspring of women given these vaccines during pregnancy (see p. 2412.1). Vaccines now in use do not contain SV40 as they are not manufactured using monkey cell cultures.

1. Stratton K, *et al.*, eds. Institute of Medicine of the National Academies. SV40 contamination of polio vaccine and cancer. *Immunization Safety Review*. Washington D.C.: National Academies Press, 2003. Also available at: http://www.nap.edu/openbook.php?isbn=0309086108 (accessed 15/07/08)

Effects on the nervous system. There have been several case reports of the isolation of poliovaccine virus from the CSF after use of oral poliomyelitis vaccine. A 7-year-old girl who had previously been vaccinated with inactivated poliomyelitis vaccine in infancy was given oral vaccine and developed prolonged headache, vomiting, and fever but no paralysis;[1] poliovirus was subsequently isolated from her CSF 34 days after she had received the oral vaccine, and it was concluded that her previous immunisations had been ineffective. In a further report,[2] poliovirus was isolated from the CSF of 2 infants with ventriculoperitoneal shunts who had developed aseptic meningitis without paralysis after oral poliomyelitis vaccination. A neurovirulent variant of Sabin type 2 oral poliomyelitis vaccine virus was detected in both the CSF and stools of an infant with transient hypogammaglobulinaemia who developed meningoencephalitis, retinitis, and irreversible hearing loss after oral poliomyelitis vaccination.[3] A 6-year-old girl given oral poliomyelitis vaccine at 1 and 2 years developed acute disseminated encephalomyelitis and a mutated form of poliovirus was isolated from her CSF;[4] it was thought that she had been infected with the mutated virus from extrafamilial contacts and that the cause of her condition may have been related to her HLA type.

1. Rantala H, *et al.* Poliovaccine virus in the cerebrospinal fluid after oral polio vaccination. *J Infect* 1989; 19: 173–6.
2. Gutierrez K, Abzug MJ. Vaccine-associated poliovirus meningitis in children with ventriculoperitoneal shunts. *J Pediatr* 1990; 117: 424–7.
3. Inaba H, *et al.* Polio vaccine virus-associated meningoencephalitis in an infant with transient hypogammaglobulinemia. *Scand J Infect Dis* 2001; 33: 630–1.
4. Ozawa H, *et al.* Acute disseminated encephalomyelitis associated with poliomyelitis vaccine. *Pediatr Neurol* 2000; 23: 177–9.

GUILLAIN-BARRÉ SYNDROME. A small cluster of cases of Guillain-Barré syndrome was seen[1] in children after a mass oral poliomyelitis vaccination campaign in Finland in 1985. An increased frequency of Guillain-Barré syndrome was also seen in adults. However, a direct link with poliovaccine virus infection could not be established and no link between Guillain-Barré syndrome and oral polio vaccine was found by a subsequent, epidemiological study in California.[2]

1. Uhari M, *et al.* Cluster of childhood Guillain-Barré cases after an oral poliovaccine campaign. *Lancet* 1989; ii: 440–1.
2. Rantala H, *et al.* Epidemiology of Guillain-Barré syndrome in children: relationship of oral polio vaccine administration to occurrence. *J Pediatr* 1994; 124: 220–3.

VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS. Although generally considered safe and effective, in extremely rare cases the live attenuated virus in oral poliomyelitis vaccines can cause vaccine-associated paralytic poliomyelitis (VAPP) in either the vaccine recipient or in a close contact. There is no such risk associated with inactivated poliomyelitis vaccines. The incidence of VAPP is about 1 case in every 2.5 million doses of vaccine and may be increased in immunocompromised patients. A case control study[1] identified intramuscular injections given within 30 days of vaccination as a risk factor in the development of VAPP. This phenomenon, known as provocation paralysis or provocation poliomyelitis, has been described with the wild virus[2] and has been recognised as a factor in vaccine-associated paralysis in the UK and USA.[3] Paralytic poliomyelitis in contacts of vaccine recipients can be further reduced by ensuring that parents without evidence of previous immunisation receive the vaccine at the same time as their children. The benefits of oral poliomyelitis vaccination are considered to greatly outweigh the small risk involved, however, and many countries where the risk of wild virus-caused poliomyelitis has been reduced to zero are now considering combined immunisation schedules with both oral and inactivated poliomyelitis vaccines. It has been suggested that inactivated poliomyelitis vaccine should be introduced globally.[4]

1. Strebel PM, *et al.* Intramuscular injections within 30 days of immunization with oral poliovirus vaccine—a risk factor for vaccine-associated paralytic poliomyelitis. *N Engl J Med* 1995; 332: 500–6.
2. Anonymous. Provocation paralysis. *Lancet* 1992; 340: 1005–6.
3. Wyatt HV. Vaccine-associated poliomyelitis. *Lancet* 1994; 343: 610.
4. Heinsbroek E, Ruitenberg EJ. The global introduction of inactivated polio vaccine can circumvent the oral polio vaccine paradox. *Vaccine* 2010; 28: 3778–83.

Precautions

As for vaccines in general, p. 2375.2.

Poliomyelitis vaccine may contain trace amounts of antibacterials such as neomycin, polymyxin B, and streptomycin and should be used with caution in patients with severe hypersensitivity to these antibacterials.

Oral poliomyelitis vaccines should not be given to patients with diarrhoea or vomiting.

Because the vaccine virus of oral poliomyelitis vaccines is excreted in the faeces for up to 6 weeks, the contacts of recently vaccinated babies and infants should be advised of the need for strict personal hygiene, particularly hand washing after napkin changing, in order to reduce the possibility of infection in unimmunised contacts. Unimmunised adults can be immunised at the same time as their children.

Immunocompromised patients are at increased risk of developing vaccine-associated paralytic poliomyelitis. Oral poliomyelitis vaccines should not be given to immunocompromised patients or their household contacts and in these persons an inactivated vaccine should be used. Asymptomatic HIV-positive persons may receive oral poliomyelitis vaccines but faecal excretion of the vaccine virus may continue for longer than in uninfected individuals. For symptomatic HIV-positive persons the use of inactivated poliomyelitis vaccine may be considered.

Intramuscular injections given after the oral vaccine may also increase the risk of vaccine-associated paralytic poliomyelitis (see above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trivalent inactivated 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)

Pregnancy. Live vaccines such as *oral poliomyelitis vaccines* are generally contra-indicated in pregnancy because of a theoretical risk to the fetus. Population-wide mass vaccination programmes become impossible, however, if pregnant mothers and women of child-bearing age are to be excluded.[1] In February 1985, mass vaccination with live oral poliomyelitis vaccine was started during a poliomyelitis outbreak in Finland.[1] Pregnant women were advised to take the vaccine. An analysis of all reported congenital malformations in the years 1982 to 1986 suggested that oral poliomyelitis vaccine had no harmful effects on fetal development as measured by overall prevalence of malformations or by the incidence of either CNS or orofacial defects. The results did not, however, exclude an effect measurable by other criteria of fetal development.

The incidence of spontaneous abortions was measured during a mass poliomyelitis vaccination campaign in Israel.[2] The number of spontaneous abortions did not differ between controls and women vaccinated during the first trimester of pregnancy; the percentage of spontaneous abortions in relation to live births was also similar. Microscopic examination of placentas from spontaneous abortions indicated no effect of oral poliomyelitis vaccine on the frequency or type of pathological changes. In addition, subsequent epidemiological study[3] found no increases in congenital malformations or in premature births during the period of and immediately after the vaccination campaign compared with those born before the campaign.

The Collaborative Perinatal Project (CPP) in the USA[4] followed up 50 897 pregnancies to examine risk factors for the development of malignancies in offspring born between 1959 and 1966. In 18 342 children whose mothers were vaccinated during pregnancy with *inactivated poliomyelitis vaccines*, there were 14 malignancies (7.6 per 10 000), while in 32 555 non-exposed children there were 10 malignancies (3.1 per 10 000). There were 7 tumours derived from neural tissue in the exposed children (3.8 per 10 000) and one in non-exposed children (0.3 per 10 000). Thus there was an excess of neural tumours but not of leukaemias or other malignancies in children exposed *in utero* to inactivated poliomyelitis vaccine. No malignancies occurred among the children born to 3056 women who received oral poliomyelitis vaccine. Serum samples collected from mothers on entry into the CPP and at delivery were subsequently analysed[5] for the presence of antibodies to Simian virus 40 (SV40). None of the serum samples from 8 mothers of infants with neural tumours had antibodies to SV40. Two of the 7 mothers of infants with leukaemia had SV40 antibodies, but only one had conversion during pregnancy. None of the samples from the 7 mothers of children with other types of cancer had antibodies. Three of 36 controls had antibodies, but in both the first and second samples. The association between use of inactivated poliomyelitis vaccine in mothers and neural tumours in their offspring could not be attributed to contamination of vaccine with SV40. A later analysis[6] of 54 796 children enrolled in the CPP found an increased risk of neural tumours and of haematological malignancy in children whose mothers were given pre-1963 poliomyelitis vaccine, but concluded that this was unlikely to have been due to transmission of SV40.

1. Harjulehto T, *et al.* Congenital malformations and oral poliovirus vaccination during pregnancy. *Lancet* 1989; i: 771–2.
2. Ornoy A, *et al.* Spontaneous abortions following oral poliovirus vaccination in first trimester. *Lancet* 1990; i: 800.
3. Ornoy A, Ben Ishai P. Congenital anomalies after oral poliovirus vaccination during pregnancy. *Lancet* 1993; 341: 1162.
4. Heinonen OP, *et al.* Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973; 2: 229–35.
5. Rosa FW, *et al.* Absence of antibody response to simian virus 40 after inoculation with killed-poliovirus vaccine of mothers of offspring with neurologic tumors. *N Engl J Med* 1988; 318: 1469.
6. Engels EA, *et al.* Poliovirus vaccination during pregnancy, maternal seroconversion to simian virus 40, and risk of childhood cancer. *Am J Epidemiol* 2004; 160: 306–16.

Interactions

As for vaccines in general, p. 2375.3.

Normal immunoglobulins. Although the use of live vaccines and immunoglobulins at the same time is generally not recommended, normal immunoglobulin had no effect on the antibody response to oral poliomyelitis vaccine when the 2 preparations were given together to 50 subjects.[1]

1. Green MS, *et al.* Response to trivalent oral-poliovirus vaccine with and without immune serum globulin in young adults in Israel in 1988. *J Infect Dis* 1990; 162: 971–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imovax Polio; Opvero; Poliorал; Sabin†; *Austral.*: Ipol; *Belg.*: Imovax Polio; *Braz.*: IPV†; *Canad.*: Imovax Polio; *China*: Imovax Polio (爱宝维); *Cz.*: Imovax Polio; IPV-Virelon†; VeroPol; *Fin.*: Imovax Polio; VeroPol; *Fr.*: Imovax Polio; *Ger.*: IPV Merieux; IPV-Virelon†; *Gr.*: Poliorix; Vaccin Antipoliomyelitique/Merieux; *Hong Kong*: Imovax Polio; *Hung.*: Imovax Polio; *India*: Imovax Polio; OPV; *Indon.*: Imovax Polio; *Israel*: Imovax Polio; Polio Sabin; *Ital.*: Imovax Polio; Poliovax-IN†; *Jpn*: Imovax Polio; *Malaysia*: Polio Sabin; *Mex.*: Polio Sabin†; Poliorал†; *Norw.*: Imovax Polio; *NZ*: Imovax Polio; Ipol; *Philipp.*: Imovax Polio; Polio Sabin; Poliorал; Poliorix†; *Pol.*: Imovax Polio; Polio Sabin†; *Port.*: Imovax Polio; *Rus.*: Imovax Polio (Имовакс Полио); Poliorix (ПОЛИОРИКС); *S.Afr.*: OPV-Merieux; Poliorал; *Singapore*: Imovax Polio; Polio Sabin; *Spain*: Vac Polio Sabin†; Vac Poliomielitica†; *Swed.*: Imovax Polio; VeroPol; *Switz.*: Poliorix; *Thai.*: Opvero; Polio Sabin; Poliorал; *Turk.*: Buccapol; OPV; Polio Sabin†; Poliorix†; *USA*: Ipol.

Pharmacopoeial Preparations

Ph. Eur.: Poliomyelitis Vaccine (Inactivated); Poliomyelitis Vaccine (Oral).

Pseudomonas Vaccines

Vacunas de pseudomonas.

Profile

Candidate *Pseudomonas aeruginosa* vaccines are under investigation for the prevention of pseudomonal infections in different disease states.

Pseudomonas aeruginosa is notably resistant to many antibacterials and there has consequently been considerable interest in developing an effective vaccine against it.[1-4] However, disappointing clinical results and improvements in antibacterial management have meant that no such vaccine is yet available for clinical use.

Early attempts in the 1960s at developing a vaccine focused on cell wall components (lipopolysaccharides). Multivalent lipopolysaccharide vaccines were tested in *animals* and in patients, including burns patients and patients with various forms of cancer and acute and chronic lung disease but, despite some positive results, these vaccines never gained clinical acceptance because of problems associated with the use of lipopolysaccharides. Vaccines designed at targeting the toxic exoproduct of *Ps. aeruginosa*, exotoxin A, produced mixed results at best; there has also been interest in exotoxin A toxoid plus other protective immunogens and in multicomponent and conjugate vaccines. There was brief interest in ribosomes and ribosomal RNA vaccines but these fell out of favour.

The discovery that motility was associated with *Ps. aeruginosa* virulence prompted research into the use of flagella as protective immunogens. The organism normally has two types of flagellum and a divalent vaccine has been tested, but with only modest benefit. There has also been some interest in development of vaccines against pili, bacterial appendages used for attachment.

Some investigators tried the use of high-molecular-weight polysaccharides as potential vaccine candidates but interest in this area has declined. Another defunct area of research is the use of pseudomonal alginate and mucoid exopolysaccharide; these were suggested for use in cystic fibrosis patients but did not progress beyond *animal* studies.

From the 1980s, there was considerable interest in the use of a variety of outer membrane proteins to develop a vaccine, partly because outer membrane proteins are exposed on the cell surface and at least one, protein F, is common to all serotypes. Encouraging results were obtained in *animal* models of infected burns and of chronic lung disease. Preliminary studies in healthy humans yielded large and sustained increases in antibody titres and found outer membrane proteins to be well tolerated. Multicomponent vaccines have been developed consisting of toxoids of known pseudomonal virulence factors such as proteases, elastases, and exotoxin A. Conjugate vaccines have been shown to be effective in *animal* models and to elicit a high antibody titre in cystic fibrosis patients.

In recent years, attention has also turned to the development of DNA vaccines, and to the use of some novel immunological approaches such as the use of pooled monoclonal antibodies directed against a variety of *Ps. aeruginosa* virulence antigens and of epitopes of pseudomonal elastase. In addition, research has shown that both active and passive immunisation with the purified type III translocation protein (PcrV) from *Ps. aeruginosa* is effective in *mouse* models of lung infection and burns, although results of combined active and passive immunisation in clinical studies were disappointing. Finally, there has been interest in obtaining immunological protection by presenting *Pseudomonas* antigens via mucous membranes, particularly in the gastrointestinal tract or intranasally.

1. Johansen HK, Gøtzsche PC. Vaccines for preventing infection with Pseudomonas aeruginosa in cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 27/08/10).
2. Cachia PJ, Hodges RS. Synthetic peptide vaccine and antibody therapeutic development: prevention and treatment of Pseudomonas aeruginosa. *Biopolymers* 2003; 71: 141–68.
3. Holder IA. Pseudomonas vaccination: a historical overview. *Vaccine* 2004; 22: 831–9.
4. Döring G, Pier GB. Vaccines and immunotherapy against Pseudomonas aeruginosa. *Vaccine* 2008; 26: 1011–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Jia Dai Bao (佳代胞); Lv Mu An (绿慕安); *Pol.*: Pseudovac.

Q Fever Vaccines

Vacunas de la fiebre Q.

Profile

A Q fever vaccine consisting of a purified killed suspension of *Coxiella burnetii* is available in Australia. It is prepared

from Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. A single 0.5-mL subcutaneous dose is given for active immunisation in individuals at high risk of Q fever. These include abattoir workers, veterinarians, farmers and others exposed to farm animals, and laboratory workers handling potentially infected tissue.

Before immunisation, patients should be tested for their serum antibody titre and a skin test performed; giving the vaccine to persons already sensitised to Q fever antigens may cause serious hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Q-Vax.

Rabies Antisera

Antisuero de la rabia; Suero antirrábico.
ATC — J06AA06.

Profile

Rabies antisera have been used to provide passive immunisation against rabies but the use of rabies immunoglobulins (see below) is preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Mirv-HDC.

Rabies Immunoglobulins

Inmunoglobulinas contra la rabia.
ATC — J06BB05.
UNII — 95F619ATQ2 (human rabies virus immunoglobulin).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Rabies Immunoglobulin; Immunoglobulinum Humanum Rabicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from donors immunised against rabies and contains specific antibodies that neutralise the rabies virus. Normal immunoglobulin may be added. It contains not less than 150 international units/mL. The liquid preparation should be stored, protected from light, in a 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.

USP 36: (Rabies Immune Globulin). A sterile solution of globulins derived from plasma or serum from selected adult human donors who have been immunised with rabies vaccine and have developed high titres of rabies antibody. It contains 10 to 18% of protein of which not less than 80% is monomeric immunoglobulin G. It has a potency of 150 international units/mL. It contains glycine as a stabilising agent, and a suitable preservative. A solution diluted to contain 1% of protein has a pH of 6.4 to 7.2. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Rabies immunoglobulins are used for passive immunisation against rabies. They are combined with active immunisation by rabies vaccines (see below) in postexposure treatment for the prevention of rabies in previously unimmunised persons who have been bitten by rabid animals or animals suspected of being rabid. There are 2 types of immunoglobulin available: human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose of HRIG is 20 international units/kg; for ERIG products it is 40 international units/kg. The recommended dose should be infiltrated in and around the cleansed wound; if infiltration of the whole volume is not possible, any remaining immunoglobulin should be given intramuscularly (in the anterolateral thigh and not the gluteal region) at a different site to that at which the vaccine was given.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Imogam Rabia; *Austral.*: Imogam; *Austria*: Berirab; *Canad.*: HyperRab; Imogam; *China*: Yi Sheng Bao Er (依生保尔); *Cz.*: Favirab; *Fr.*: Favirab; Imogam Rage; *Ger.*: Berirab; Tollwutglobulin; *Gr.*: Berirap; *Hong Kong*: Berirab; HyperRab; *India*: Berirab-P; Carig; Equirab; Erig; HRIG; Imogam Rabies; Imorab; *Indon.*: Imogam; *Israel*: Berirab; HyperRab; Imogam Rabies; KamRab; *Mex.*: Berirab-P; Kamrab†; *Philipp.*: BayRab; Berirab-P; Equirab; Favirab; *S.Afr.*: Rabigam; *Spain*: Imogam Rabia; *Switz.*: Berirab; *Thai.*: Berirab; Favirab; Imogam Rabies†; KamRAB; TRCS ERIG; *Turk.*: BayRab; Favirab; Imogam†; *USA*: HyperRab; Imogam Rabies.

Pharmacopoeial Preparations
Ph. Eur.: Human Rabies Immunoglobulin;
USP 36: Rabies Immune Globulin.

Rabies Vaccines

Vacunas de la rabia.
ATC — J07BG01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Rabies Vaccine for Human Use Prepared in Cell Cultures; Vaccinum Rabiei ex Cellulis ad Usum Humanum; Rabies Vaccine BP 2014). A sterile freeze-dried suspension of inactivated rabies virus; a suitable strain is grown in an approved cell culture. The cell-culture medium may contain suitable antibacterials at the smallest effective concentration. The vaccine is prepared immediately before use by the addition of a suitable sterile liquid. The estimated potency is not less than 2.5 international units per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Rab may be used on the label.

Uses and Administration

Rabies vaccines are used for active immunisation against rabies. They are used as part of postexposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Infection does not take place through unbroken skin but is possible through uninjured mucous membranes and has been reported after the inhalation of virus in the laboratory. Rabies vaccines are also used for pre-exposure prophylaxis against rabies in persons exposed to a high risk of being bitten by rabid or potentially rabid animals.

Schedules for prophylaxis and treatment of rabies are recommended by WHO (see Pre-exposure Immunisation and Postexposure Treatment, p. 2414.1) and many countries have immunisation schedules based on these.

In the UK, two types of rabies vaccine are available. The first type is prepared from inactivated Wistar rabies virus strain PM/WI38 1503-3M cultured on human diploid cells, and the second type is prepared from inactivated Flury LEP virus strain produced on purified chick embryo cells. Each contains not less than 2.5 international units/mL. The purified chick embryo-cell vaccine is given intramuscularly into the deltoid region in adults but into the anterolateral aspect of the thigh in children. The human diploid-cell vaccine is given intramuscularly into the deltoid region in both adults and children. Other cell culture-derived vaccines, such as Vero cell rabies vaccine, are available in other countries.

For **pre-exposure prophylaxis** against rabies, the recommended schedule in the UK is 3 doses, each of 1 mL, by intramuscular injection on days 0, 7, and 28; the third dose may in some instances be given on day 21 if there is insufficient time before travel. For persons at regular and continuous risk, a single reinforcing dose should be given 1 year after completion of the primary course with further doses at 3- to 5-year intervals. For those at intermittent risk, a booster dose should be given from 2 years after completion of the primary course.

For **postexposure treatment**, thorough cleansing of the wound with soap and water is imperative. The recommended schedule in the UK for unimmunised or incompletely immunised persons is 5 doses, each of 1 mL, by intramuscular injection on days 0, 3, 7, 14, and 30. (In some countries 4-dose regimens are favoured, see p. 2414.1.) In fully immunised persons two doses of vaccine should be given intramuscularly, one each on day 0 and day 3. Vaccination should be started as soon as possible after exposure, and may be stopped if it is proved that the patient was not at risk. In previously unimmunised patients at high risk, rabies immunoglobulin (see above) should also be given at the same time as the first dose of vaccine.

Rabies. Rabies is caused by infection with a rhabdovirus of the genus Lyssavirus. Rabies has a worldwide distribution, mainly in domesticated and wild dogs but also in bats and other warm-blooded animals, although some countries, including the UK, most of Australasia, and Antarctica are designated as rabies-free areas. Transmission of the rabies virus to humans is usually by the bite of an infected animal or contamination of broken skin by saliva. Infection is possible via intact mucous membranes and by aerosol transmission, but infection is unlikely after contamination of intact skin. Other body fluids such as urine and tears should be regarded as potentially infectious; rabies virus transmission has also been reported after organ transplantation from misdiagnosed donors.

Human rabies is almost always fatal once symptoms have appeared. The incubation period varies from 2 weeks to 6 years (average of 2 to 3 months) depending on the distance of the bite site from the brain and the amount of virus in the inoculum. There are 2 types of clinical presentations of rabies; encephalitic (furious) and paralytic (dumb). Encephalitic rabies presents with periods of hyperexcitability accompanied by severe agitation and bizarre behaviour alternating with periods of lucidity. Severe spasms of the larynx and pharynx may be provoked by attempts at swallowing (leading to hydrophobia) or by air blown at the face (aerophobia). Other symptoms include hypersalivation, fever, and convulsions. In the paralytic form, progressive flaccid paralysis develops in the bitten limb and ascends in a symmetrical or asymmetrical manner. Patients not dying through respiratory or cardiac arrest during the acute phase may develop various complications culminating in coma and death or (very rarely) recovery; only a few patients are documented as having survived after the onset of coma, and all had received either pre- or postexposure immunisation.

National control programmes involve epidemiological surveillance, mass canine immunisation campaigns, and dog population management. The development of oral animal vaccines delivered on baited food has met with considerable success in some areas and has become an essential tool for eliminating rabies in wild animals. Rigorously applied controls of international transfer of animals including certification of vaccination and quarantine for animals entering rabies-free areas are necessary to prevent re-introduction of rabies.

Although some treatments have been tried including antivirals, interferons, high doses of rabies immunoglobulin, and corticosteroids, none has shown evidence of efficacy. Postexposure treatment after contact with a suspected or confirmed rabid animal may be effective in preventing death; it includes prompt and thorough cleansing of the contaminated site and the early use of rabies vaccine with or without rabies immunoglobulins. For a brief outline of postexposure treatment, see p. 2414.1.

Pre-exposure prophylaxis is recommended in persons at high risk of exposure, either due to their occupation or those travelling in enzootic areas. The main obstacle to mass pre-exposure vaccination appears to be the high cost of cell culture vaccines. See under Pre-exposure Immunisation (p. 2414.1) for outlines of recommended vaccination schedules.

CHOICE OF VACCINES. Many different rabies vaccines are available for human use. Some are derived from nerve tissue of animals; some from avian tissues (duck embryos), and some prepared in cell cultures. The first rabies vaccine was based on attenuated virus from desiccated nerve tissue. Later, inactivated nervous tissue-derived vaccines were prepared from rabid sheep, goat (Semple vaccines) or suckling mouse brains (Feunzalida Palacios vaccine). A complete postexposure treatment course of nerve-tissue vaccine consists of up to 23 injections and is associated with severe neurological reactions and a significant failure rate. WHO therefore strongly recommends that nerve-tissue vaccines should not be used, and that production should be stopped. Cell-derived rabies vaccines were subsequently developed; the human diploid cell rabies vaccine (HDCV) was introduced in 1967 and later less expensive purified chick embryo-cell vaccine (PCECV) and purified Vero-cell rabies vaccines (PVRV) entered use. There appears to be little difference in terms of safety and antigenicity between HDCV, PCECV, and PVRV in recommended regimens. The incidence of severe hypersensitivity reactions should, however, be lower with PVRV and PCECV than with HDCV since the purification process removes most human serum albumin in the cell-growth medium before virus inactivation (see Hypersensitivity, under Adverse Effects and Precautions, p. 2414.3). A purified duck-embryo vaccine (PDEV) provided similar efficacy and safety to vaccines produced from cell cultures, but is no longer manufactured.

There are few data concerning the efficacy of rabies vaccines. It appears that nerve-tissue vaccines afford limited protection after minor exposures to rabies virus, are less effective after head bites, and are of little use after very severe exposures. Failure rates for HDCV, PCECV, and PVRV (including cases with less than the recommended therapy) have been estimated as less than 1 in 80 000 treatments in the USA, Canada, and Europe, 1 in 12 000 to 20 000 in Thailand, and 1 in 30 000 in the remaining tropical countries. Reported failures of these vaccines are usually associated with severe lesions on or near the head and/or errors in treatment, such as deviation from recommendations, incorrect site of vaccine administration, or delay in treatment. WHO recommends a minimum potency of

2.5 international units per intramuscular dose for all cell-derived rabies vaccines.

The cost of cell-derived rabies vaccines is prohibitively high in the developing world. Although the adverse effects of nerve-tissue vaccines preclude their use for pre-exposure prophylaxis, they are still used in some countries for postexposure prophylaxis. WHO is anxious that nerve-tissue vaccines should be replaced with affordable cell-derived vaccines as soon as possible. In the meantime, cost-cutting regimens have been devised for use of cell-derived rabies vaccines by the intradermal route. Rapid immunisation is achieved by the use of several sites of injection; fewer injections are required than with traditional intramuscular regimens.

PRE-EXPOSURE IMMUNISATION. WHO[1,2] has developed guidelines as to who should receive pre-exposure vaccination with rabies vaccines. However, national policies may vary somewhat from that of WHO, depending on the local risk of contracting rabies and the vaccines available; it is generally recommended for use in persons at high risk of infection with rabies virus. Where available, the vaccines produced in cell culture or from purified embryonated eggs are preferred over the vaccines produced in animal tissues (see under Choice of Vaccine, p. 2413.3). WHO recommends[1,2] pre-exposure prophylaxis for persons regularly at high risk of exposure, such as certain laboratory workers, veterinarians, animal handlers, and wildlife officers, and those living in or travelling to areas where rabies is endemic (particularly in children under 15 years of age). The immunisation schedule should preferably consist of 3 injections of a rabies vaccine of potency at least 2.5 international units given on days 0, 7, and either day 21 or 28, but variation of a few days is unimportant. Vaccine should be given into the deltoid area of the arm or for young children into the anterolateral area of the thigh. Titres of virus-neutralising antibodies can be checked in serum samples collected 1 to 3 weeks after the last dose. Those who work with the live virus should have their antibody titres checked every 6 months and if the figure falls below 0.5 international units/mL they should receive a booster.[1,2] Other individuals at continuing risk should have their titres checked every 12 months and a booster given if the titre is below 0.5 international units/mL.[1] Where serological testing is unavailable, a booster vaccination every 5 years may be an acceptable alternative.[2]

WHO also suggests intradermal use of rabies vaccine in doses of 0.1 mL on days 0, 7, and either day 21 or 28 but intramuscular injection is preferable and is mandatory in those taking malaria prophylaxis.

In the UK,[3] the schedule for immunisation (see Uses and Administration, p. 2413.2) is similar to that recommended by WHO.

In the USA, immunisation with a human diploid cell vaccine or a purified chick embryo cell vaccine is carried out similarly to the WHO schedule, with serum-antibody titres determined every 6 months to 2 years, depending upon the level of exposure, and booster doses given as necessary. Vaccines for intradermal use are no longer available in the USA.[4]

1. WHO. *Current WHO guide for rabies pre and post-exposure prophylaxis in humans* (revised December 2007, June 2009). Available at: http://www.who.int/rabies/PEP_prophylaxis_guidelines_June09.pdf (accessed 14/12/09)
2. WHO. Rabies vaccines. WHO position paper. *Wkly Epidem Rec* 2007; 82: 425–35. Also available at: http://www.who.int/wer/2007/wer8249_50.pdf (accessed 14/12/09) Correction *ibid.* 2008; 83: 15–16.
3. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_0799177?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 27/08/10)
4. CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; 57 (RR-3): 1–28. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5703.pdf (accessed 14/12/09)

POSTEXPOSURE TREATMENT. WHO guidelines[1,2] emphasise the importance of prompt local treatment for all bite wounds and scratches that may be contaminated with rabies virus and that, depending on the category of animal contact, rabies vaccine on its own or with rabies immunoglobulin should be given. The combination of these measures immediately after exposure is considered to guarantee almost complete protection. Pregnancy and infancy are not contra-indications to postexposure vaccination. These measures should be instituted even in patients who present months after having been bitten.

First aid or local treatment consists of immediate thorough flushing and washing of the wound with water, or soap and water, or detergent followed by the application of alcohol 70% or tincture or aqueous solution of iodine. Medical care may then consist of the instillation of rabies immunoglobulin into the depth of the wound and infiltration around the wound. Ideally the wound should not be sutured, but if suturing is necessary then it is essential that it be preceded by rabies immunoglobulin as above. Antimicrobials and tetanus vaccine may also be given as necessary.

The use of rabies vaccine and of rabies immunoglobulin depends on the category of animal contact. WHO classifies the type of contact with a suspect or rabid animal into 3 categories:

- category I covers touching or feeding of animals and licks on intact skin
- category II covers nibbling of uncovered skin, minor scratches or abrasions without bleeding
- category III covers single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membranes with the animal's saliva, and exposure to bats

Generally no treatment is required for category I contact. Patients who have had category II contact should be given rabies vaccine but the course may be stopped if the contact has been with a cat or dog that remains healthy throughout an observation period of 10 days or if postmortem study of the contact animal shows it to be negative for rabies. Immunocompromised patients with category II contact should also be given rabies immunoglobulin. Patients with category III contact should be given rabies vaccine preceded by rabies immunoglobulin infiltrated around the wound and instilled into it as described above.

There are 2 types of immunoglobulin available; human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose for HRIG is 20 international units/kg and for ERIG products is 40 international units/kg. As much as possible of the dose should be infiltrated into and around the wound, with the remainder being injected intramuscularly into a site remote from that where vaccine was given, such as the anterior thigh.

The potency of rabies vaccines should be at least 2.5 international units per single human dose. For intramuscular vaccination schedules one dose should be given on days 0, 3, 7, 14, and 28 into the deltoid region or, for small children, into the anterolateral area of the thigh. An abbreviated multisite intramuscular schedule (the 2-1-1 regimen) induces an early antibody response and may be particularly effective when postexposure treatment has not included a rabies immunoglobulin. This schedule consists of one dose given in the right arm and one in the left arm on day 0, and one dose intramuscularly into the deltoid region on days 7 and 21.

Intradermal vaccination reduces the volume of injection required and is therefore suited to situations where vaccine or money is in short supply. For intradermal vaccination one dose (0.1 mL) of purified chick embryo-cell or purified Vero-cell vaccine may be given at each of two sites, usually the left and right upper arm, on days 0, 3, 7, and 28. Alternatively, in emergency situations when no rabies immunoglobulin is available, either human diploid cell or purified chick embryo-cell rabies vaccine may be given intradermally in one dose at each of 8 sites on day 0, in one dose at 4 sites on day 7, and subsequently in one dose at one site on days 28 or 30 and 90.

For postexposure treatment of previously vaccinated patients, WHO recommends local treatment of wounds followed by rabies vaccine given on days 0 and 3, either as a standard intramuscular dose or as one intradermal dose per site. No rabies immunoglobulin should be given. Patients who previously received vaccines of unproven potency or who have failed to develop an acceptable rabies neutralising antibody titre should be given full treatment as for those previously unimmunised.

In the UK,[3] rabies immunoglobulin is given if the patient is previously unimmunised and at high risk. Vaccine is given on days 0, 3, 7, 14, and 30 (five doses) in unimmunised persons (although the UK licensed product information for human diploid cell vaccine also recommends a sixth dose on day 90); two doses, one each on day 0 and day 3 are given to previously fully immunised persons.

In the USA, a human diploid-cell vaccine or a purified chick embryo cell vaccine may be used for postexposure treatment.[4] In previously unimmunised individuals, a 5-dose intramuscular regimen similar to that of WHO was formerly recommended,[4] but with increasing evidence of the value of an abbreviated 4-dose regimen[5] the CDC now recommends[6] a 1-mL dose of vaccine intramuscularly on days 0, 3, 7, and 14, with rabies immunoglobulin as in the WHO schedule. In previously immunised individuals, two doses of vaccine are given on days 0 and 3, and rabies immunoglobulin is not required.

1. WHO. *Current WHO guide for rabies pre and post-exposure prophylaxis in humans* (revised December 2007, June 2009). Available at: http://www.who.int/rabies/PEP_prophylaxis_guidelines_June09.pdf (accessed 14/12/09)
2. WHO. Rabies vaccines. WHO position paper. *Wkly Epidem Rec* 2007; 82: 425–35. Also available at: http://www.who.int/wer/2007/wer8249_50.pdf (accessed 14/12/09) Correction. *ibid.* 2008; 83: 15–16.
3. DoH. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_0799177?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 27/08/10)
4. CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; 57 (RR-3): 1–28. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5703.pdf (accessed 14/12/09)
5. Rupprecht CE, *et al.* Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine* 2009; 27: 7141–8.
6. CDC/ACIP. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2010; 59 RR-2: 1–9. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5902.pdf (accessed 30/04/10)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Patients receiving human diploid-cell or purified chick embryo-cell rabies vaccines may have pain, erythema, and induration at the injection site. Systemic reactions including abdominal pain, diarrhoea, nausea and vomiting, headache, chills, dizziness, fever, malaise, convulsions, encephalitis, lymphadenopathy, arthralgia and myalgia, dyspnoea and wheezing, or rash may also occur. Reactions may become more severe with repeated doses. Hypersensitivity reactions including anaphylaxis occur more commonly with vaccines prepared from non-human sources than with human diploid-cell vaccine. However, these reactions have also been associated with the presence of β-propiolactone-altered human albumin in the human diploid-cell vaccine.

Neurological reactions (meningoencephalitis, meningoencephalomyelitis, mononeuritis multiplex, transverse myelitis, or ascending paralysis) have been associated with the use of animal nerve-tissue vaccines. WHO considers that nerve-tissue vaccines should no longer be used. There are only isolated reports of neurological reactions after use of human diploid-cell vaccines.

Patients known to be hypersensitive to a particular vaccine or its components should be given an alternative product if available, although there are no absolute contra-indications to postexposure treatment. Pre-exposure prophylaxis should be delayed in patients with febrile illness until fever has resolved.

Effects on the nervous system. Rabies vaccines were originally prepared from infected animal brain tissue. The incidence of neurological complications with these vaccines was about 1 in 1 600, with an overall mortality of 15%.[1] Neurological adverse effects were attributed to myelin basic proteins present in these vaccines.[1-4] Subsequently, a highly immunogenic rabies vaccine was produced from the relatively myelin-free nerve tissue of suckling mice. However, neuroparalytic complications were reported in about 1 in 8 000 persons treated.[1,5] Most of these complications were of a Guillain-Barré-type illness, and had a fatality rate of 20 to 50%.[1]

Neuroparalytic reactions occur less frequently (1 in 32 000 persons treated) with vaccines prepared from duck embryo tissue;[1,5] however, these vaccines are no longer manufactured.[5]

Cell-derived rabies vaccines have been developed with better safety profiles.[1,5,6]

Isolated cases of neuroparalytic reactions have been reported with human diploid-cell or chick embryo-cell vaccines, mostly manifesting as a Guillain-Barré-type illness.[1,7-10]

1. Bernard KW, *et al.* Neuroparalytic illness and human diploid cell rabies vaccine. *JAMA* 1982; 248: 3136–8.
2. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
3. Kulkarni V, *et al.* Biphasic demyelination of the nervous system following anti-rabies vaccination. *Neurol India* 2004; 52: 106–8.
4. Siddiqui A, *et al.* Guillain-Barre syndrome occurring after rabies vaccination. *J Pakistan Med Assoc* 2005; 55: 87–8.
5. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; 77: 109–19.
6. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2004. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
7. Knitzel T, *et al.* Guillain-Barré syndrome and human diploid cell rabies vaccine. *Lancet* 1989; i: 1334–5.
8. Tornatore CS, Richert JR. CNS demyelination associated with diploid cell rabies vaccine. *Lancet* 1990; 335: 1346–7.
9. Mortiere MD, Falcone AL. An acute neurologic syndrome temporally associated with postexposure treatment of rabies. *Pediatrics* 1997; 100: 720–1.
10. Chakravarty A. Neurologic illness following post-exposure prophylaxis with purified chick embryo cell antirabies vaccine. *J Assoc Physicians India* 2001; 49: 927–8.

Hypersensitivity. Systemic hypersensitivity reactions[1] have occurred in up to 6% of patients receiving booster immunisation with human diploid-cell rabies vaccine (HDCV), with onset after 2 to 21 days. Presenting features include generalised or pruritic rash or urticaria, angioedema, arthralgias, fever, nausea, and vomiting. These reactions have been linked to the presence of β-propiolactone-altered human albumin in HDCV. A lower risk of hypersensitivity reaction should exist with newer cell-derived vaccines that contain little or no human albumin, such as purified chick embryo cell rabies vaccines (PCECV) or purified Vero-cell rabies vaccines (PVRV). A review[2] noted that patients given booster immunisation with PCECV did not generally have systemic hypersensitivity reactions; data from the US Vaccine Adverse Event

Reporting System covering 336 reported adverse events to PCECV between October 1997 and December 2005 included only 20 reports classified as possible anaphylaxis, of which only 3 were considered serious.[3] In a comparison study[4] involving 400 children, patients receiving a new chromatographically purified Vero-cell vaccine were found to have a lower incidence of systemic hypersensitivity (0.7%) than those in the HDCV group (1.2%) after booster immunisation.

1. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; 77: 109–19.
2. Dreesen DW. A global review of rabies vaccines for human use. *Vaccine* 1997; 15 (suppl): S2–S6.
3. Dobardzic A, *et al.* Safety review of the purified chick embryo cell rabies vaccine: data from the Vaccine Adverse Event Reporting System (VAERS), 1997–2005. *Vaccine* 2007; 25: 4244–51.
4. Sabchareon A, *et al.* A new Vero cell rabies vaccine: results of a comparative trial with human diploid cell rabies vaccine in children. *Clin Infect Dis* 1999; 29: 141–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rabies 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)

Spongiform encephalopathies. Possible transmission of Creutzfeldt-Jakob disease associated with sheep-brain rabies vaccine has been reported from India.[1] It was suggested that transmission of the abnormal prion protein from sheep with scrapie might be implicated.

1. Arya SC. Acquisition of spongiform encephalopathies in India through sheep-brain rabies vaccination. *Natl Med J India* 1992; 4: 311–12.

Interactions

As for vaccines in general, p. 2375.3.

Antimalarials. Studies have suggested that continuous antimalarial chemoprophylaxis with *chloroquine* during primary immunisation with human diploid-cell rabies vaccine, given intradermally for pre-exposure prophylaxis, may be associated with a poor antibody response.[1,2] WHO[3] recommends that people currently taking malaria prophylaxis or those unable to complete the 3-dose rabies pre-exposure regime before starting malaria prophylaxis should receive pre-exposure rabies vaccination by the intramuscular route instead.

1. Taylor DN, *et al.* Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* 1984; i: 1405.
2. Pappaioanou M, *et al.* Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med* 1986; 314: 280–4.
3. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Verorab; *Austral.*: Rabipur; *Austria*: Rabipur; *Belg.*: Rabipur; *Braz.*: HDCV†; Vacina Anti-Rabica Humana†; *Canad.*: Imovax Rabies; RabAvert; *Chile*: Lyssavac N; Verorab; *China*: Fu Er Bo (福尔博); Rabipur (瑞必补尔); Verorab (维尔博); Wu Sheng Wang Ning (武生旺宁); *Cz.*: Rabipur; Verorab; *Denm.*: Rabies-Imovax; Rabipur; *Fin.*: Rabies-Imovax; *Fr.*: Rabipur; *Ger.*: Rabipur; Tollwut-Impfstoff (HDC); *Hong Kong*: Verorab; *India*: Imovax Rabies; Rabipur; Rabivax; *Indon.*: Verorab; *Israel*: Rabipur; Verorab; *Ital.*: Imovax Rabbia†; Rabipur; *Malaysia*: Verorab; *Neth.*: Rabipur; *Norw.*: Rabies-Imovax; Rabipur; *NZ*: Verorab; *Philipp.*: Abhayrab; Indirab; Lyssavac N; Rabiesvax; Rabipur; Speeda; V-Rab; Verorab; *Pol.*: Verorab; *Port.*: Rabipur; *Rus.*: Rabipur (Рабипур); *S.Afr.*: Rabipor; Verorab; *Singapore*: Rabipur; *Spain*: Rabipur; Vacuna Antirrabica; *Swed.*: Rabies-Imovax; *Switz.*: Rabipur; *Thai.*: Abhayrab; Lyssavac N†; Rabipur; Rabivax; Speeda; Verorab; *Turk.*: HDCV†; Rabivac; *UK*: Rabipur; *USA*: Imovax Rabies; RabAvert; *Venez.*: Verorab.

Pharmacopoeial Preparations

Ph. Eur.: Rabies Vaccine for Human Use Prepared in Cell Cultures.

Raxibacumab *(USAN, rINN)*

Raxibacumabum; Раксибакумаб.

Immunoglobulin, G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), disulfide with human monoclonal PA λ-chain, dimer.

CAS — 565451-13-0.

UNII — 794PGL549S.

NOTE. The name ABthrax has been used as a trade mark for raxibacumab.

Uses and Administration

Raxibacumab is a monoclonal antibody that neutralises the toxin secreted by *Bacillus anthracis* by binding to its protective antigen. Raxibacumab has not been tested in humans with anthrax; its efficacy is based on *animal* studies. It is used with antibacterials for the treatment of inhalation anthrax (p. 173.2), and for prophylaxis where no alternative therapy exists.

Raxibacumab is given intravenously as a single dose of 40 mg/kg. It is diluted using sodium chloride 0.9% to a final volume of 250 mL and given over 2 hours and 15 minutes. The infusion rate is 15 mL/hour for the first 20 minutes and then increased to 125 mL/hour for the remainder of the dose. Diphenhydramine should be given up to 1 hour before the infusion to reduce the incidence and severity of infusion reactions; however, if a reaction occurs the infusion may be slowed or interrupted.

For use in children, see below.

References.
1. Mazumdar S. Raxibacumab. *MAbs* 2009; 1: 531–8.
2. Migone T-S, *et al.* Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med* 2009; 361: 135–44.
3. Anonymous. Raxibacumab for anthrax. *Med Lett Drugs Ther* 2013; 55: 27–8.

Administration in children. Raxibacumab is given intravenously as a single dose based on body-weight:

- less than or equal to 15 kg: 80 mg/kg
- greater than 15 kg to 50 kg: 60 mg/kg
- greater than 50 kg: the usual adult dose is given, see above

Raxibacumab is diluted with sodium chloride 0.45% or 0.9% to a volume ranging from 7 to 250 mL depending on the weight of the child. The infusion is given over about 2 hours and 15 minutes; it is given slowly for the first 20 minutes and then the infusion rate may be increased for the remainder of the dose. Diphenhydramine should be given up to 1 hour before the infusion; if a reaction does occur then the infusion should be slowed or interrupted.

Adverse Effects and Precautions

Raxibacumab commonly causes infusion reactions including rash, urticaria, and pruritus, and it is recommended that diphenhydramine is given up to 1 hour before treatment. Other common adverse effects are pain in the extremities and somnolence. Less common effects include anaemia, leucopenia, lymphadenopathy, palpitations, flushing, hypertension, peripheral oedema, vasovagal syncope, vertigo, fatigue, insomnia, back pain, and muscle spasms. Increases in blood amylase and creatine phosphokinase concentrations, and prolonged prothrombin time have been seen.

Pharmacokinetics

There is some tissue distribution of raxibacumab after intravenous infusion, but it does not cross the blood-brain barrier. Raxibacumab has a half-life of about 20 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Raxibacumab Injection.

Respiratory Syncytial Virus Immunoglobulins

Inmunoglobulinas contra el virus sincitial respiratorio.

Palivizumab *(BAN, rINN)*

MEDI-493; Palivitsumabi; Palivizumaburn; Паливизумаб.

Immunoglobulin G1 (human-mouse monoclonal MEDI-493 γ1-chain antirespiratory syncytial virus protein F), disulfide with human-mouse monoclonal MEDI-493 κ-chain, dimer.

CAS — 188039-54-5.

ATC — J06BB16.

UNII — DQ448MW7KS.

Uses and Administration

Respiratory syncytial virus immunoglobulin (RSVI) is available in some countries for the passive immunisation of infants against lower respiratory-tract infections caused by RSV. It is prepared from the pooled plasma of adults selected for high titres of antibodies that neutralise the virus. Each mL of RSVI contains about 50 mg of protein.

In the USA, children under 2 years of age with chronic lung disease of prematurity (bronchopulmonary dysplasia) or a history of premature birth have received a prophylactic intravenous infusion once a month during the RSV season (typically November to April or early May). The drug has been given in a dose of up to 750 mg/kg at an initial rate of 75 mg/kg per hour for 15 minutes, followed by 180 mg/kg per hour until the end of the infusion.

Palivizumab, a humanised monoclonal antibody to RSV, is available in some countries for the prevention of RSV in premature infants (born at 35 weeks of gestation or less) and in children less than 2 years of age needing treatment for chronic lung disease of prematurity, as well as those with haemodynamically significant congenital heart disease. It is used intramuscularly in a dose of 15 mg/kg monthly during the RSV season. Ideally the first dose should be given before the start of the RSV season; up to 5 doses are usually given. Children undergoing cardiac bypass should be given an extra dose of palivizumab as soon as they are stable after surgery; doses are subsequently resumed monthly thereafter.

The American Academy of Pediatrics has issued revised indications for the use of palivizumab which no longer include recommendations for the use of respiratory syncytial virus immunoglobulin (RSVI).[1] Palivizumab prophylaxis should be considered for infants younger than 2 years of age with chronic lung disease of prematurity (bronchopulmonary dysplasia) who have required medical therapy for their condition within 6 months of the anticipated start of the RSV season. Infants born before 32 weeks 0 days gestation may also benefit from prophylaxis even if they do not have chronic lung disease. Palivizumab, may in addition be given to children under 2 years of age with haemodynamically significant congenital heart disease. Although prophylaxis has been shown to reduce hospitalisation for infants born between 32 and 35 weeks gestation, the cost for this large group of infants should be considered carefully. In general, the AAP recommends a maximum of 5 doses for all infants with haemodynamically significant congenital heart disease, chronic lung disease, or birth before 32 weeks 0 days gestation. In infants with a gestational age of between 32 weeks 0 days and 34 weeks 6 days who do not have haemodynamically significant congenital heart disease or chronic lung disease, prophylaxis has been restricted to those at higher risk; AAP now recommends a maximum of 3 doses in this group if they are born within 3 months of or during the RSV season and either attend child care or one or more other children in the household are under 5 years of age. Doses are only recommended while children are below 3 months of age.

In the UK, the Joint Committee on Vaccination and Immunisation[2] recommends a maximum of 5 doses of palivizumab in certain classes of premature infant depending on their chronological age at the start of the RSV season and gestational age, as follows:

- those with chronic lung disease
  - born at less than 35 weeks of gestation and with a chronological age of 1 to < 1.5 months
  - born at 32 weeks of gestation or less and with a chronological age of 1.5 to 3 months
  - born at 28 weeks of gestation or less and with a chronological age of 3 to 6 months
  - born at 24 weeks of gestation or less and with a chronological age of 6 to 9 months
- haemodynamically significant, acyanotic congestive heart disease
  - born at 32 weeks of gestation or less and with a chronological age of < 1.5 months
  - born at 30 weeks of gestation or less and with a chronological age of 1.5 to 3 months
  - born at 26 weeks of gestation or less and with a chronological age of 3 to 6 months

They also advise that palivizumab be given during the RSV season to children under the age of 24 months who have severe combined immunodeficiency syndrome (until immune reconstituted) and to long-term ventilated children aged less than 12 months (or less than 24 months with additional co-pathology) at the start of the RSV season.

Both palivizumab and RSVI have been shown to decrease the risk of severe RSV infection in high-risk infants and children. Palivizumab is preferred over RSVI for most high-risk children because of its comparative ease of administration, safety, and efficacy (the latter is no longer available in the USA). Monthly use of palivizumab during the RSV season results in a 45 to 55% reduction in hospitalisation. Although palivizumab is usually preferred, RSVI may also decrease the incidence of other respiratory-tract infections in addition to those caused by RSV, and this may be of benefit for infants younger than 6 months who are not eligible for influenza immunisation and those with severe pulmonary disease who may be more prone to other respiratory-tract infections. Palivizumab has not been shown to affect the rate of hospitalisation for non-RSV infections or the incidence of otitis media.

1. Committee on Infectious Diseases of the American Academy of Pediatrics. Policy statements–modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009; 124: 1694–1701. Also available at: http://pediatrics.aappublications.org/cgi/reprint/124/6/1694 (accessed 17/12/09)
2. DoH. Joint Committee on Vaccination and Immunisation statement on immunisation for respiratory syncytial virus (issued 11th October 2010). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_120395.pdf (accessed 30/11/10)

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies palivizumab 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.

There is some evidence that antibody responses to diphtheria, tetanus, pertussis, and Haemophilus influenzae vaccines may be reduced in infants also receiving respiratory syncytial virus immunoglobulins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Synagis; *Austral.*: Synagis; *Austria*: Synagis; *Belg.*: Synagis; *Braz.*: Synagis; *Canad.*: Synagis; *Chile*: Synagis; *Cz.*: Synagis; *Denm.*: Synagis; *Fin.*: Synagis; *Fr.*: Synagis; *Ger.*: Synagis; *Gr.*: Synagis; *Hong Kong*: Synagis; *Hung.*: Synagis; *Irl.*: Synagis; *Israel*: Abbosynagis; *Ital.*: Synagis; *Jpn*: Synagis; *Malaysia*: Synagis; *Mex.*: Synagis; *Neth.*: Synagis; *Norw.*: Synagis; *NZ*: Synagis; *Pol.*: Synagis; *Port.*: Synagis; *Rus.*: Synagis (Синагис); *S.Afr.*: Synagis; *Singapore*: Synagis; *Spain*: Synagis; *Swed.*: Synagis; *Switz.*: Synagis; *Turk.*: Synagis; *UK*: Synagis; *USA*: RespiGam†; Synagis; *Venez.*: Synagis.

Respiratory Syncytial Virus Vaccines

Vacunas del virus sincitial respiratorio.

Profile

Vaccines containing RSV protein subunit are being studied for active immunisation.

Development of an effective and safe vaccine against RSV has been hampered by several factors.[1-3] The target population for a vaccine is mainly young infants who may not respond adequately to vaccination owing to the antigenic diversity of RSV, immunological immaturity, or the presence of maternal antibodies. In the early 1960s, a formalin inactivated respiratory syncytial virus vaccine known as FI-RSV (also sometimes called Lot 100) was tested in infants and children aged 2 months to 7 years but failed to protect against subsequent infection with wild-type virus; it also led to a catastrophically exaggerated clinical response to wild-type virus in infants who were naive to RSV before vaccination, resulting in hospitalisation for the majority of recipients and 2 fatalities. Since that time, some candidate vaccines have subsequently been developed including live attenuated virus and viral protein subunit vaccines.[1,2] Several of the live attenuated vaccine candidates have been investigated in humans but results have generally been disappointing. More recently, genetically engineered live attenuated vaccine candidates have been generated, and some are currently being investigated in clinical studies.[1,2]

Subunit vaccines are composed of the F and G glycoproteins from RSV since these are the glycoproteins that induce antibody responses.[1,2] They are most likely to be of use in older persons and in high-risk children and might also be used for maternal immunisation. A chimeric FG fusion protein vaccine was evaluated in phase I studies but is no longer in development.

1. Durbin AP, Karron RA. Progress in the development of respiratory syncytial virus and parainfluenza virus vaccines. *Clin Infect Dis* 2003; 37: 1668–77.
2. Kneyber MCJ, Kimpen JLL. Advances in respiratory syncytial virus vaccine development. *Curr Opin Investig Drugs* 2004; 5: 163–70.
3. Power UF. Respiratory syncytial virus (RSV) vaccines—two steps back for one leap forward. *J Clin Virol* 2008; 41: 38–44.

Rift Valley Fever Vaccines

Vacunas de la fiebre del valle del Rift.

Profile

An inactivated rift valley fever vaccine has been developed for the active immunisation of persons at high risk of contracting the disease.

Rotavirus Vaccines

Vacunas de rotavirus.

ATC — J07BH01; J07BH02.

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

Ph. Eur. 8: (Rotavirus Vaccine (Live, Oral); Vaccinum Rotaviri Vivum ad Peroralia). A preparation of one or more suitable virus serotypes, grown in an approved cell substrate and presented in a form suitable for oral administration. The vaccine is a clear liquid or it may be a freeze-dried preparation to be reconstituted immediately before use, as stated on the label, to give a slightly turbid liquid. The vaccine ready for administration may be coloured owing to the presence of a pH indicator. The vaccine is formulated so as to avoid inactivation by gastric fluids. It should be stored at 2 degrees to 8 degrees, and be protected from light.

Uses and Administration

Several live oral rotavirus vaccines for use in the prevention of childhood diarrhoea have been developed and some are now licensed. Since April 2009, the WHO Strategic Advisory Group of Experts (SAGE) on immunisation has recommended that rotavirus vaccines be included in all national childhood immunisation programmes.

A live attenuated oral monovalent rotavirus vaccine (based on the human RIX4414 strain) is available in some countries. Two doses are given, the first at 6 weeks of age onwards and the subsequent dose at least 4 weeks later; the course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks. A live oral pentavalent reassortant rotavirus vaccine (based on human and bovine strains) is also available in the USA. Three doses are given, the first at 6 to 12 weeks of age and the two subsequent doses at 4- to 10-week intervals; the third dose should not be given after 32 weeks of age.

A live oral tetravalent rotavirus vaccine (RRV-TV) was formerly available in the USA but was withdrawn by the manufacturer in October 1999 after reports of intussusception associated with its use.

Guidelines and recommendations.

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 23/05/13)
2. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009; 58 (RR-2): 1–25. Correction. *ibid.* 2010; 59: 1074. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5802.pdf (accessed 23/05/13)
3. Committee on Infectious Diseases. American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics* 2009; 123: 1412–20. Also available at: http://pediatrics.aappublications.org/cgi/reprint/123/5/1412 (accessed 23/05/13)
4. WHO. Rotavirus vaccines: WHO position paper–January 2013. *Wkly Epidem Rec* 2013; 88: 49–64. Also available at: http://www.who.int/wer/2013/wer8803.pdf (accessed 23/05/13)

References.

1. Vesikari T, *et al.* Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; 354: 23–33.
2. Ruiz-Palacios GM, *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; 354: 11–22.
3. Buttery JP, Kirkwood C. Rotavirus vaccines in developed countries. *Curr Opin Infect Dis* 2007; 20: 253–8.
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5. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008; 21: 198–208.
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8. Plosker GL. Pentavalent rotavirus vaccine (RotaTeq): a review of its use in the prevention of rotavirus gastroenteritis in Europe. *Drugs* 2010; 70: 1165–88.
9. Soares-Weiser K, *et al.* Vaccines for preventing rotavirus diarrhoea: vaccines in use. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2012 (accessed 23/05/13).

Vaccine development. Rotaviruses are an important cause of severe diarrhoea in both developed and developing countries (see Gastro-enteritis, p. 951.3); rates of illness are similar in both and improvement in water quality and general hygiene does not have much effect on viral transmission. The disease infects almost all children before the age of 5 years but is most severe among children 4 to 23 months of age.[1] Human rotavirus diarrhoea is caused by group A, B, or C rotaviruses.[2] While an initial infection does not produce complete immunity, it does appear to be protective against further severe gastroenteritis. Vaccination therefore aims to produce a similar effect.[1,3] Development of a suitable vaccine has been made difficult by the diversity of rotaviruses.[2] Initial attempts at vaccine development used single bovine or rhesus monkey strains but these were associated with variable efficacy and adverse effects.[4-6]

To overcome these problems reassortant rotavirus (RRV) strains were constructed. These combined animal rotavirus strains with human rotavirus genes coding for serotype-specific antigens, enabling polyvalent vaccines to be produced against the major rotavirus serotypes causing disease. Some such candidate vaccines are under development[7] and some are now licensed.[8]

1. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009; 58 (RR-2): 1–25. Correction. *ibid.* 2010; 59: 1074. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5802.pdf (accessed 17/12/09)
2. Anonymous. Puzzling diversity of rotaviruses. *Lancet* 1990; 335: 573–5.
3. Committee on Infectious Diseases. American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics* 2009; 123: 1412–20. Also available at: http://pediatrics.aappublications.org/cgi/reprint/123/5/1412 (accessed 17/12/09)
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5. Bernstein DI, *et al.* Evaluation of WC3 rotavirus vaccine and correlates of protection in healthy infants. *J Infect Dis* 1990; 162: 1055–62.
6. Flores J, *et al.* Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants. *Lancet* 1987; i: 882–4.
7. Glass RI, *et al.* The future of rotavirus vaccines: a major setback leads to new opportunities. *Lancet* 2004; 363: 1547–50.
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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

The most common adverse effects reported in subjects receiving rotavirus vaccines (attenuated monovalent human strain or pentavalent reassortant rotavirus vaccine) are fever, fatigue, irritability, and gastrointestinal disturbances. Otitis media, nasopharyngitis, bronchospasm, and haematochezia (blood in the stools) have also been reported with the pentavalent vaccine. A few cases of Kawasaki disease have been reported with the pentavalent vaccine but no causal relationship has been established.

There has been much debate on the causal role of rotavirus vaccines for intussusception (see below); cases have been reported since marketing.

Both the attenuated monovalent human strain vaccine and the pentavalent reassortant vaccine are contra-indicated in infants with a history of intussusception, with congenital malformations of the gastrointestinal tract, or with severe combined immunodeficiency (SCID) disorder. Caution is also generally advised in those with gastrointestinal illnesses, growth retardation, or who are immunocompromised, and use may be postponed in children suffering from diarrhoea or vomiting. Use of a rotavirus vaccine should be carefully considered before being given to infants with a close family contact who is immunocompromised; if given precautions should be taken to avoid transmission of any excreted vaccine virus.

Intussusception. A live oral tetravalent vaccine (RRV-TV) became available in the USA in August 1998 but was withdrawn from the market by the manufacturer in October 1999 after reports of intussusception (a condition when part of the intestine prolapses into the lumen of an adjacent part causing an obstruction). From September 1998 until July 1999, 15 patients with intussusception had been reported to the Vaccine Adverse Event Reporting System (VAERS), 12 of whom developed symptoms within a week of vaccination.[1] While this evidence was considered inconclusive, further studies were expected to clarify the risks associated with routine use of this vaccine. One such study,[2] in which 429 infants with intussusception were retrospectively analysed, found that 74 (17.2%) had received RRV-TV compared with 226 of 1763 controls (12.8%) and concluded that there was evidence of a causal relationship with the vaccine. Another retrospective study,[3] however, found that there was no evidence of an increase in hospital admissions due to intussusception during the period of RRV-TV availability and recommended that a large, randomised, double-blind vaccine study be performed to determine the absolute risk. Further analysis of the incidence of intussusception associated with RRV-TV has prompted discussion as to whether the absolute risk might in fact be sufficiently low that withholding the vaccine results in greater mortality than would be caused by intussusception.[4] Reassessment of the data on RRV-TV and intussusception has suggested that the risk for intussusception was age-dependent; relative risk for intussusception following the first dose of RRV-TV increased with increasing age.[5,6] However, WHO Global Advisory Committee on Vaccine Safety found that there was insufficient evidence available to determine whether use of RRV-TV before 60 days of age was associated with a lower risk for intussusception but confirmed the association of a high risk of intussusception in infants immunised after day 60.[7] Such considerations have implications for the ongoing evaluation of other candidate live attenuated rotavirus vaccines in that, should cases of intussusception occur, a decision might be required as to what constitutes an acceptable rate.[4]

From February 2006 until February 2007, 35 patients with confirmed intussusception had been reported to VAERS after vaccination with the pentavalent reassortant vaccine; 17 of whom developed symptoms within 21 days of vaccination, including 11 that occurred within 7 days of vaccination. However, this number of cases is not higher than the age adjusted background rates for intussusception.[8]

The safety of the currently marketed mono- and pentavalent live vaccines has been reviewed.[9]

1. CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR* 1999; 48: 577–81.
2. Murphy TV, *et al.* Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001; 344: 564–72. Correction. *ibid.*: 1564.
3. Simonsen L, *et al.* Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet* 2001; 358: 1224–9.
4. Murphy BR, *et al.* Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. *J Infect Dis* 2003; 187: 1301–8.
5. Rothman KJ, *et al.* Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. *J Infect Dis* 2006; 193: 898.
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7. WHO. Global Advisory Committee on Vaccine Safety, 1–2 December 2005. *Wkly Epidem Rec* 2006; 81: 15–19.
8. CDC. Postmarketing monitoring of intussusception after RotaTeq® vaccination—United States, February 1, 2006–February 15, 2007. *MMWR* 2007; 56: 218–22.
9. Patel MM, *et al.* Intussusception and rotavirus vaccination: a review of the available evidence. *Expert Rev Vaccines* 2009; 8: 1555–64.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rotarix; RotaTeq; *Austral.*: Rotarix; RotaTeq; *Austria*: Rotarix; RotaTeq; *Belg.*: Rotarix; RotaTeq; *Canad.*: Rotarix; RotaTeq; *Chile*: Rotarix; *China*: Luo Te Wei (罗特威); *Cz.*: Rotarix; RotaTeq; *Denm.*: Rotarix; RotaTeq†; *Fr.*: Rotarix; RotaTeq; *Ger.*: Rotarix; RotaTeq; *Gr.*: Rotarix; RotaTeq; *Hong Kong*: Rotarix; RotaTeq; *Hung.*: Rotarix; RotaTeq; *Irl.*: Rotarix; RotaTeq; *Israel*: Rotarix; RotaTeq; *Ital.*: Rotarix†; RotaTeq; *Jpn*: Rotarix; RotaTeq; *Malaysia*: Rotarix; RotaTeq; *Mex.*: Rotarix; *Neth.*: Rotarix; RotaTeq; *Norw.*: Rotarix; RotaTeq; *NZ*: Rotarix; RotaTeq; *Philipp.*: Rotarix; RotaTeq; *Pol.*: Rotarix; RotaTeq; *Port.*: Rotarix; RotaTeq; *S.Afr.*: Rotarix; *Singapore*: Rotarix; RotaTeq; *Spain*: Rotarix†; RotaTeq; *Swed.*: Rotarix; RotaTeq; *Switz.*: Rotarix; *Thai.*: Rotarix; RotaTeq; *Turk.*: Rotarix; RotaTeq; *UK*: Rotarix; *Ukr.*: Rotarix (Ротарикс); *USA*: Rotarix; RotaTeq; *Venez.*: Rotarix.

Rubella Immunoglobulins

Inmunoglobulinas contra la rubéola.
ATC — J06BB06.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Human Rubella Immunoglobulin; Immunoglobulinum Humanum Rubellae). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the rubella virus. Normal immunoglobulin may be added. It contains not less than 4500 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Uses and Administration

Rubella immunoglobulins may be used for passive immunisation against rubella (German measles). They have been used to prevent or modify rubella in susceptible persons.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Human Rubella Immunoglobulin.

Rubella Vaccines

Vacunas de la rubéola.
ATC — J07BJ01.
UNII — 52202H034Z (rubella virus live antigen); U751HEX436 (rubella virus antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Rubella Vaccine (Live); Vaccinum Rubellae Vivum). A freeze-dried preparation of a suitable live attenuated strain of rubella virus grown in human diploid cell cultures. It is reconstituted immediately before use. The cell-culture medium may contain a permitted antibacterial at the smallest effective concentration, and a suitable stabiliser may be added to the bulk vaccine. The final vaccine contains not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Rubella may be used on the label.

Uses and Administration

Rubella vaccines are used for active immunisation against rubella (German measles). The symptoms of rubella infection are generally mild except in the early stages of pregnancy when it leads to fetal damage in most infants.

For primary immunisation combined measles, mumps, and rubella vaccine (p. 2400.2) is usually given. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Women of child-bearing age should also be vaccinated with the combined vaccine if they are seronegative; women who are found to be seronegative during pregnancy should be vaccinated in the early postpartum period. Effective precautions against pregnancy must be observed for at least one month after vaccination. To avoid the risk of transmitting rubella to pregnant patients, all health service staff, both male and female, should be screened and those found to be seronegative should be vaccinated.

In some countries, a single-antigen rubella vaccine has been used although combined vaccines are usually preferred.

References.

1. WHO. Rubella vaccines: WHO position paper. *Wkly Epidem Rec* 2000; 75: 161–69. Also available at: http://www.who.int/immunization/wer7520rubella%20_May00_position_paper.pdf (accessed 30/06/10)

Adverse Effects

As for vaccines in general, p. 2375.1.

Generally, adverse effects have not been severe. Those occurring most commonly are rashes, pharyngitis, fever, and lymphadenopathy; arthralgia and arthritis may also occur. Thrombocytopenia (including immune thrombocytopenia) has been reported rarely.

Effects on bones and joints. Although acute arthralgia or arthritis occurs in up to 30% of women after rubella vaccination,[1] a retrospective analysis found no evidence of an increased risk of chronic arthropathies.[2]

1. Tingle AJ, *et al.* Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 1997; 349: 1277–81.
2. Ray P, *et al.* Risk of chronic arthropathy among women after rubella vaccination. *JAMA* 1997; 278: 551–6.

Effects on hearing. For a report of irreversible sensorineural deafness associated with use of measles and rubella vaccine, see p. 2400.3.

Effects on the nervous system. For a report of optic neuritis in 2 children after use of measles and rubella vaccine, see under Adverse Effects of Measles and Rubella Vaccines, p. 2400.1.

Precautions

As for vaccines in general, p. 2375.2.

Rubella vaccines should not be given during pregnancy. In the UK it is recommended that patients should be advised not to become pregnant within 1 month of vaccination. However, no case of congenital rubella syndrome has been reported after the inadvertent use of rubella vaccines shortly before or during pregnancy and there is no evidence that the vaccines are teratogenic. Inadvertent use of rubella vaccines during pregnancy should not therefore result in a recommendation to terminate the pregnancy. There is no risk to a pregnant woman from contact with recently vaccinated persons as the vaccine virus is not transmitted.

Rubella vaccines are not generally recommended for children below the age of 1 year in whom maternal antibodies might prevent a response.

Vaccines may contain traces of neomycin and/or polymyxin and should therefore not be given to individuals with a history of anaphylaxis to these antibacterials.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rubella 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)

Pregnancy. Since 1971 the US CDC has followed up women given rubella vaccines within 3 months before or after conception.[1] Up to 1979 vaccines containing either the Cendehill or HPV-77 strains of rubella virus were available. None of the 290 infants born to the 538 women given these vaccines had defects indicative of congenital rubella syndrome; this included 94 live-born infants of women who were known to be susceptible to rubella before receiving the vaccine. In 1979 a rubella vaccine containing the Wistar RA 27/3 strain was introduced. None of 212 infants born live to 254 women known to be susceptible to rubella and who had received the RA 27/3 rubella vaccine from 1979 to 1988 had defects indicative of congenital rubella syndrome. These results are consistent with experiences in Germany[2] and the UK.[3,4] However, because of evidence that rubella vaccine viruses can cross the placenta and infect the fetus a theoretical risk to the fetus cannot be completely ruled out.[1] Thus in both the UK and USA pregnancy is considered a contra-indication to rubella vaccination, and patients are also advised not to become pregnant within one month of vaccination. However, in neither country is termination of pregnancy recommended if the vaccine is inadvertently given during pregnancy.

1. Anonymous. Rubella vaccination during pregnancy—United States, 1971–1988. *JAMA* 1989; 261: 3374–83.
2. Enders G. Rubella antibody titers in vaccinated and nonvaccinated women and results of vaccination during pregnancy. *Rev Infect Dis* 1985; 7 (suppl 1): S103–S107.
3. Sheppard S, *et al.* Rubella vaccination and pregnancy: preliminary report of a national survey. *BMJ* 1986; 292: 727.
4. Tookey PA, *et al.* Rubella vaccination in pregnancy. *Commun Dis Rep* 1991; 1(review 7): R86–R88.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rudivax; *Austral.*: Ervevax†; Meruvax II; *China*: Rudivax (护贝法); *Fr.*: Rudivax; *Gr.*: Rubeaten; Vaccin Rubeole; *India*: R-Vac; *Israel*: Rudivax; *Mex.*: Ervevax†; *NZ*: Ervevax; *Port.*: Rudivax†; *Rus.*: Ervevax (Эрвевакс)†; Rudivax (Рудивакс); *S.Afr.*: Rudivax†; *UK*: Almevax; *USA*: Meruvax II†.

Pharmacopoeial Preparations
Ph. Eur.: Rubella Vaccine (Live).

Rubella and Mumps Vaccines

Vacunas de la rubéola y la parotiditis; Vacunas de la rubéola y las paperas.
ATC — J07BJ51.

Uses and Administration

Rubella and mumps vaccines have been used for active immunisation although for primary immunisation a combined measles, mumps, and rubella vaccine (p. 2400.2) is usually used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

See also under Mumps Vaccines, p. 2402.3, and Rubella Vaccines, above.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Biavax II†.

Schistosomiasis Vaccines

Bilharzia Vaccines; Vacunas de la esquistosomiasis.

Profile

Vaccines against schistosomiasis are under development.

Despite attempts since the 1960s, development of an effective vaccine against schistosomiasis has proved difficult.[1,2] The worms themselves are not thought to be responsible for the disease but the eggs elicit a powerful and damaging immune response when they are trapped in tissue.

As only the very young in endemic areas will not have been exposed to schistosomiasis a protective antigen for a candidate vaccine must be one that will attack the adult parasite without cross reacting with egg antigens thus increasing the risk of developing chronic disease in those already affected. Most antigen vaccine candidates tested to date have at best resulted in 50 to 60% protection in *animal* models although repeated immunisation with irradiated cercariae in *murine* models has resulted in almost 80%

protection. Consequently it has been questioned whether sterilising immunity should be the aim. It might be more realistic to develop a vaccine which can reduce the overall worm burden and the fecundity of surviving worms, thus reducing the number of eggs released and deposited in the liver. This in turn would lead to lower rates of infection by reducing the numbers of miracidia available to infect snails. Such a vaccine would, however, only be effective in terms of infection and morbidity rates after a considerable period of time, probably more than 20 years. Alternatively, vaccine candidates that specifically attack particular stages of the parasite life cycle might be feasible. Some potential vaccine candidate antigens have been identified and clinical studies have taken place with the glutathione-*S*-transferase antigen from *S. haematobium*, Sh28 GST. Use of antigens with recombinant cytokines in order to enhance immune response, or with the B subunit of cholera toxin in order to suppress harmful inflammatory responses, has also been investigated. There is also some suggestion that it might be possible to develop a multicomponent vaccine consisting of multiple antigens that will give protection against different stages in the parasite cycle.[1]

1. Lebens M. *et al.* Current status and future prospects for a vaccine against schistosomiasis. *Expert Rev Vaccines* 2004; 3: 315–28.
2. McManus DP, Loukas A. Current status of vaccines for schistosomiasis. *Clin Microbiol Rev* 2008; 21: 225–42.

Scorpion Venom Antisera

Antídoto contra las picaduras de escorpión o alacrán; Antisuero contra el veneno de escorpión; Scorpion Antivenins; Scorpion Antivenoms.

Uses and Administration

Some scorpion stings are dangerous and even fatal. The use of a scorpion venom antiserum suitable for the species of scorpion can prevent symptoms, provided that it is given with the least possible delay; other general supportive measures and symptomatic treatment are also needed. The efficacy of scorpion venom antisera is disputed by some clinicians.

Scorpion stings. Scorpion stings are common throughout the tropics, but the most dangerous and potentially fatal species are found in India, North Africa and the Middle East, the southern states of North America and Mexico, Latin America and the Caribbean, and southern Africa. Local symptoms after scorpion stings include intense pain and swelling. Systemic symptoms result from excitation of nerve and muscle cells by the venom; the pattern of symptoms depends upon the species of scorpion. Symptoms such as hypersalivation, vomiting, and diarrhoea are generally followed by adrenergic features, with release of catecholamines producing hypertension, toxic myocarditis, arrhythmias, heart failure, and pulmonary oedema. The cardiotoxic effects are prominent features of stings in India, North Africa, and the Middle East. Neurotoxic effects such as fasciculations, spasms, and respiratory paralysis are seen with stings from North American species. Stings by the black scorpion of Trinidad may also produce pancreatitis.

Pain is treated with local infiltration or peripheral nerve block with local anaesthetics; opioid analgesics may be necessary, but are regarded as dangerous after stings by some North American species. An appropriate antiserum may be given as soon as possible after envenomation, although the efficacy of some antisera has been questioned and in some countries they are no longer considered of benefit. Supportive treatment for cardiotoxic effects includes alpha blockers, calcium-channel blockers, and ACE inhibitors. The use of cardiac glycosides, beta blockers, and atropine is controversial. Phenobarbital and benzodiazepines have been suggested for neurotoxic effects.

References.
1. el Amin EO, *et al.* Scorpion sting: a management problem. *Ann Trop Paediatr* 1991; 11: 143–8.
2. Bond GR. Antivenin administration for Centruroides scorpion sting: risks and benefits. *Ann Emerg Med* 1992; 21: 788–91.
3. Warrell DA, Fenner PJ. Venomous bites and stings. *Br Med Bull* 1993; 49: 423–39.
4. Müller GJ. Scorpionism in South Africa: a report of 42 serious scorpion envenomations. *S Afr Med J* 1993; 83: 405–11.
5. Gateau T, *et al.* Response to specific centruroides sculpturatus antivenom in 151 cases of scorpion stings. *Clin Toxicol* 1994; 32: 165–71.
6. Sofer S, *et al.* Scorpion envenomation and antivenom therapy. *J Pediatr* 1994; 124: 973–8.
7. Karalliedde L. Animal toxins. *Br J Anaesth* 1995; 74: 319–27.
8. Abroug F, *et al.* Serotherapy in scorpion envenomation: a randomised controlled trial. *Lancet* 1999; 354: 906–9.
9. Isbister GK, *et al.* Scorpion stings in Australia: five definite stings and a review. *Intern Med J* 2004; 34: 427–30.
10. Gazarian KG, *et al.* Immunology of scorpion toxins and perspectives for generation of anti-venom vaccines. *Vaccine* 2005; 23: 3357–68.
11. Bencheikh RS, *et al.* Conduite à tenir devant une piqûre de scorpion au Maroc. *Ann Fr Anesth Reanim* 2008; 27: 317–22.
12. Boyer LV, *et al.* Arizona Envenomation Investigators. Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med* 2009; 360: 2090–8.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Alacramyn; *USA*: Anascorp.

Shigella Vaccines

Dysentery Vaccines; Shigellosis Vaccines; Vacunas contra Shigella; Vacunas de la disentería; Vacunas de la shigellosis.

Profile

Shigella vaccines have been under investigation since the 1960s but early prototypes were unsatisfactory. Live attenuated oral vaccines, parenteral conjugated vaccines, and intranasal vaccines are now also under development.

Natural or experimental exposure to *Shigella* antigens has been shown to induce clinical immunity, and there has been some work towards developing an effective vaccine.[1,2] There have been 3 main approaches to vaccination under investigation.[1] Firstly, workers at the USA National Institutes of Health have developed a series of vaccines in which the O antigen of *S. sonnei*, *S. flexneri* 2a strain, or *S. dysenteriae* type 1 is conjugated to *Pseudomonas aeruginosa* recombinant exoprotein A. These vaccines are given intramuscularly and have elicited strong immune responses in adults and children tested, and some have reached phase III studies. A second approach has been to deliver *Shigella* lipopolysaccharide intranasally in proteasomes, which are purified outer membrane proteins that form a multimolecular vesicular complex around the antigen; these vaccines are being tested in phase I studies. The third approach is the use of live attenuated oral vaccines, attenuated by creating deletions in genes that govern vital metabolic processes within the organism or by mutating genes that encode specific virulence factors.

A major challenge in the development of a shigella vaccine is to provide protection against all of the many serotypes that appear epidemiologically important. Most experts agree that for a shigella vaccine to be totally effective globally it must protect against *S. dysenteriae* type 1, *S. sonnei*, and all 15 classical *S. flexneri* serotypes. However, it has been shown that a composite of 3 *S. flexneri* serotypes (2a, 3a, and 6) can provide cross protection against the remaining 12. Hence the ultimate plan is to develop a pentavalent vaccine comprising these 3 *S. flexneri* serotypes with *S. sonnei* and *S. dysenteriae* type 1.[1] Shigella vaccines have been licensed for use in China.[2]

1. Kotloff KL. Progress in Shigella vaccine development. In: de Quadros CA, ed. *Vaccines: Preventing Disease and Protecting Health*. Washington D.C., 2004: 130–9.
2. Kweon MN. Shigellosis: the current status of vaccine development. *Curr Opin Infect Dis* 2008; 21: 313–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Shigelat (Шигелат).

Smallpox Vaccines

Vacunas de la viruela.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Smallpox Vaccine (Live)). A liquid or freeze-dried preparation of live vaccinia virus grown in the membranes of the chick embryo, in cell cultures, or in the skin of living animals. The cell culture medium may contain suitable antibacterials at the lowest effective concentration. Store at 2 degrees to 8 degrees and protect from light. The liquid vaccine should not be allowed to freeze.

Uses and Administration

After the global eradication of smallpox in 1980, vaccination against smallpox (using first generation vaccinia virus vaccine) has been indicated for those considered to be at high risk such as laboratory workers handling certain orthopoxviruses, and key emergency, healthcare, and military personnel who may have to respond to a bioterrorist release of smallpox. A second generation smallpox vaccine has been licensed in the USA for inclusion to the National Stockpile for vaccination of those considered to be at high risk for smallpox infection. Persons at high risk and who have received primary vaccination against smallpox, should be re-vaccinated every 3 to 10 years depending on their exposure risk. Vaccination is not recommended for persons working with highly attenuated strains of orthopoxviruses.

WHO considers that mass vaccination against smallpox is currently not appropriate, although individuals who may be at risk of exposure to smallpox or those with confirmed infection may be vaccinated.

Recombinant vaccinia viruses are being investigated as vectors of foreign antigens, for example in a candidate AIDS vaccine (p. 2376.1).

Vaccine development. Smallpox[1] is an acute contagious and sometimes fatal disease caused by variola virus, a member of the Poxviridae family and of the orthopoxvirus genus. There is substantial cross-protection between poxviruses of the same genus; the very effective first generation smallpox vaccine used in the global vaccination programme was created from an orthopoxvirus, vaccinia. In 1980 WHO declared smallpox to have been globally eradicated.

There has since been concern that smallpox may be used as a terrorist weapon (although WHO considers this risk to be extremely low in most countries). Therefore, research into safer vaccines against smallpox has continued. First generation vaccine was produced from vaccinia strains grown on the skin of live animals or calf lymph. Despite purification processes, the vaccine contained some bacteria, animal proteins, and adventitious animal viruses, and produced a high incidence of adverse effects, some of which were extremely serious (see Adverse Effects and Precautions, below). Second generation vaccines are single clones of vaccinia isolated from the set of genetically related viruses that made up the first generation ones; they are grown in tissue culture (rather than on animal skin or calf lymph) and are free of bacteria and adventitious animal viruses. A second generation vaccine has been found to be effective and is licensed in the USA for inclusion to the National Stockpile. However, this vaccine still has a high incidence of adverse effects. Third generation vaccines[2] are in the early stages of development. They are being developed from vaccinia strains attenuated by serial passage on non-human tissue or by genetic manipulation, and are expected to be safer than either first or second generation vaccines. Interest has also been shown in monoclonal variola antibodies for passive immunisation.[1,3]

Stocks of smallpox (variola) virus are being kept in a few secure laboratories in the USA and Russia. Since the eradication of smallpox, WHO maintains a stockpile of smallpox vaccine, and recommends vaccination for people with occupational exposure to fully potent orthopoxviruses, such as certain laboratory and healthcare workers. Because of concern that smallpox may be used for bioterrorism, WHO and several countries have increased the number of doses kept in stock.[1] Policies for the use of smallpox vaccine, including bioterrorism preparedness, have been developed in many countries such as the USA[4,5] and UK[6,7] with some countries recommending vaccination for key emergency and military personnel.

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Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Both first and second generation live smallpox vaccines have been associated with a high incidence of adverse effects. The most common adverse effects are injection site reactions, fatigue, fever, headache, malaise, myalgia, erythema, and generalised rash. Rarely there may be generalised vaccinial infection, or severe skin or CNS infection resulting in encephalitis, encephalomyelitis, encephalopathy, necrotising skin infection (progressive vaccinia, vaccinia necrosum, vaccinina gangrenosum, or disseminated vaccinia), eczema vaccinatum, and erythema multiforme (including Stevens-Johnson syndrome). Fatalities have occurred, particularly from post-vaccination encephalitis and progressive vaccinia. Inadvertent contamination of other body sites (such as the face, mouth, nose, lips, and genitalia) from the site of vaccination also occurs frequently; autoinoculation of the eye (ocular vaccinia)

may result in blindness. Benign and malignant lesions have also been reported at the vaccination site.

There have been reports of myocarditis or pericarditis or both, including some fatalities, associated with smallpox vaccination. Smallpox vaccination is not recommended for infants under 12 months of age, for persons with a history of eczema or other skin conditions, those who are immunocompromised, for pregnant women, or for women who breast feed. Household contacts of these groups should also not be vaccinated. Vaccination is best avoided in persons with known cardiac disease.

References.
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2. CDC. Notice to readers: supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2003; 52 (RR-07): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5207.pdf (accessed 05/11/07)
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: En Zai Shi (恩再适); *USA*: ACAM2000; Dryvax†.

Pharmacopoeial Preparations
Ph. Eur.: Smallpox Vaccine (Live).

Snake Venom Antisera

Antídoto contra las mordeduras de serpiente; Antisuero contra el veneno de serpiente; Snake Antivenins; Snake Antivenoms.

ATC — J06AA03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Viper Venom Antiserum, European; Immunoserum Contra Venena Viperarum Europaearum). A preparation containing the specific antitoxic globulins that have the power of neutralising the venom of one or more species of viper (*Vipera ammodytes*, *V. aspis*, *V. berus*, or *V. ursinii*). The globulins are obtained by fractionation of the serum of animals that have been immunised against the venom or venoms. Each mL neutralises the venoms in not less than 100 mouse LD_{50} of *V. ammodytes*, 100 of *V. aspis*, 50 of *V. berus*, or 50 of *V. ursinii*. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that the only poisonous snake native to the British Isles is the adder or common viper, *Vipera berus*. In a geographical region where other species of snake (including elapids) are found, antisera able to neutralise the venoms of the species of snake indigenous to the region should be used. When the preparation is intended to neutralise the venom or venoms of one or more snakes other than vipers, the title Snake Venom Antiserum is used.

Uses and Administration

Venomous snakes comprise the Viperidae (vipers), Elapidae (cobras, kraits, and mambas), and the Hydrophiidae (sea snakes).

The venom of snakes is a complex mixture chiefly of proteins, many of which have enzymatic activity, and may provoke local inflammatory reactions. The venom may have profound effects on tissue, blood vessels and other organs, blood cells, coagulation, and myotoxic or neurotoxic effects with sensory, motor, cardiac, renal, and respiratory involvement.

Snake venom antisera are the only specific treatment available for venomous snake bites, but can produce severe adverse reactions. They are generally only used if there are clear indications of systemic involvement, severe local involvement, or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. Adrenaline should be available in case of anaphylactic reactions to the antiserum; premedication with adrenaline, corticosteroids, and/or antihistamines is widely practiced but is regarded as controversial.

In Great Britain, the only indigenous poisonous snake is the adder, *Vipera berus*; its bite is rarely fatal but European Viper Venom Antiserum (or Zagreb antivenom) may sometimes be indicated as part of the overall treatment. The usual dose for adults and children is 10 mL by intravenous injection over 10 to 15 minutes or by intravenous infusion over 30 minutes after diluting in 5 mL/kg body-weight of sodium chloride 0.9%; the dose may be repeated after about 1 to 2 hours if symptoms of systemic envenoming persist.

In the USA, a polyvalent crotalidae antiserum against *Bothrops atrox*, *Crotalus adamanteus*, *C. atrox*, and *C. durissus terrificus*, and an antiserum against the North American coral snake, *Micrurus fulvius*, are available. In Australia, polyvalent antisera against the brown snake, death adder, taipan, and tiger snake, plus either the king brown snake or black snake, are available. A variety of polyvalent and monovalent antisera are also available as appropriate to the indigenous species of snakes in many other countries.

Snake bites. Most snake species are non-venomous and belong to the colubrid family although a few colubrids are technically venomous. The 3 families of venomous front-fanged snakes are the elapids, vipers, and sea snakes. Elapids include cobras, mambas, kraits, coral snakes, and the Australasian venomous land snakes. Vipers are subdivided into crotalids (pit vipers) and viperids. Viper bites are much more common than elapid bites, except in Australasia, where vipers do not occur naturally. Sea snake bites occur among fishermen of the Asian and western Pacific coastal areas. Although there are some notable exceptions, viper bites tend to cause vasculotoxicity, elapids cause neurotoxicity, and sea snakes cause myotoxicity.

Only a few snakes are known to be of medical importance. Of the vipers these include *Bothrops atrox* (Central and South America), *Bitis arietans* (Africa), *Echis carinatus* (Africa and Asia), *Vipera russelli* (Asia), and *Agkistrodon rhodostoma* (south-east Asia). In a few restricted areas of Africa and Asia, cobra bites are common; bites by mambas (Africa) and kraits (Asia) are rare. The carpet viper, *Echis pyramidum*, and saw-scaled viper, *Echis carinatus*, can justifiably be labelled the most dangerous snakes in the world and they cause more deaths and serious poisoning than any other snake.

Management of snake bite involves general supportive care and monitoring of vital functions but in systemic snake-bite poisoning, specific snake venom antiserum is the most effective therapeutic agent available. If used correctly, it can reverse systemic poisoning when given hours or even days after the bite. It is highly desirable to wait for clear clinical evidence of systemic poisoning before giving an antiserum and therefore it should not be given routinely in all cases of snake bite. Monospecific antisera are more effective, and less likely to cause reactions, than polyvalent antisera. The dosage of antiserum to be used is dependent on the species of snake and the consequent potency of the requisite antiserum. The antiserum should be given intravenously diluted in isotonic saline, either by infusion or bolus injection (see under Adverse Effects and Precautions, below). First aid measures including incisions and suction to remove the venom and application of tourniquets are generally to be discouraged. In most cases, the bitten limb should be immobilised and the victim transferred to a medical facility, with the snake if possible. For bites by elapids, when respiratory failure may occur before the patient reaches hospital, a tourniquet may be justified to delay the onset of neurotoxicity. Supportive treatment is necessary even in patients who have received an adequate dose of antiserum. Local pain may be treated with a suitable analgesic. Artificial respiration may be required in patients with symptoms of neurotoxicity. Anticholinesterases may be of benefit against the neurotoxic effects of some snake venoms and it has been recommended that an intravenous test dose of edrophonium preceded by atropine should be tried in patients with severe symptoms of neurotoxicity. For those patients who respond, treatment with neostigmine should be started but anticholinesterases are unlikely to affect outcome in patients who already require assisted respiration. Hypovolaemia should be corrected cautiously with parenteral fluids. Hypotension may be treated with subcutaneous adrenaline or, in patients bitten by Russell's viper, a response to dopamine has been noted. Patients with renal impairment may require dialysis if they do not respond to rehydration, diuretics, and dopamine. Broad spectrum antibacterials and a tetanus vaccine should be given as prophylactic measures. Surgical decompression and debridement of necrotic tissue may be necessary once normal haemostasis has been restored.

References.
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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Serum sickness is not uncommon and anaphylactic reactions may occur.

Anaphylaxis. Conjunctival or cutaneous hypersensitivity testing failed to predict early (anaphylactic) reactions to the antivenom given in a study of patients in Nigeria with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*) and in Thailand with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T. macrops*), the monocellate Thai cobra (*Naja kaouthia*), or the Malayan pit viper (*Calloselasma rhodostoma*). It was considered that conventional hypersensitivity testing has no predictive value for the occurrence of allergic reactions to antivenom and that it is not justifiable to delay treatment for 20 or 30 minutes to read the results of these tests. Although the rate at which antiserum can be given is more easily controlled by intravenous infusion, this method has serious practical disadvantages in the rural tropics where most cases of snake bite occur and an advantage of the intravenous push injection is that the person giving the antiserum must remain with the patient during the period when most severe anaphylactic reactions develop.

Pretreatment with low-dose subcutaneous adrenaline may reduce the incidence of anaphylaxis and other acute adverse reactions to the antiserum.[1] However, premedication with adrenaline, antihistamines, and corticosteroids, although widely practiced, is controversial. In one study,[2] prophylaxis with promethazine was ineffective in preventing anaphylaxis from antiserum against *Bothrops* envenomation.

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2. Fan HW, *et al.* Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; 318: 1451–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Suero Antiofídico Polivalente; *Austral.*: Black Snake Antivenom; Polyvalent Snake Antivenom; *Fr.*: Viperfav; *Hong Kong*: Sea Snake Antivenene; Tiger Snake; *India*: Antisnake Venom; ASVS; *Mex.*: Antivipmyn; Coralmyn; *Singapore*: Polyvalent Snake Antivenom; Sea Snake Antivenom; *USA*: CroFab.

Multi-ingredient Preparations. *Hung.*: Crotalgin Forte; Crotalgin; Kovitox.

Pharmacopoeial Preparations
Ph. Eur.: European Viper Venom Antiserum.

Spider Venom Antisera

Antídoto contra el veneno de las arañas; Antisuero contra el veneno de arañas; Spider Antivenins; Spider Antivenoms.

Uses and Administration

The use of a spider venom antiserum suitable for the species of spider can prevent symptoms, provided that it is done with the least possible delay; other general supportive measures and symptomatic treatment may also be needed.

The symbol † denotes a preparation no longer actively marketed

An antiserum against the black widow spider (*Latrodectus mactans*) is available in the USA and Canada. The contents of a vial containing at least 6000 antivenin units is the usual dose for adults and children. In severe cases and in children under 12 years of age it is given by intravenous infusion in sodium chloride 0.9% over 15 minutes; in less severe cases, it may be given by intramuscular injection.

Antivenoms are also available against other *Latrodectus* species, including the Australian red-back spider (*L. hasselti*) and the South African button spiders. An antiserum against the funnel-web spider (*Atrax robustus*) is available in Australia.

Antivenoms have also been developed against *Loxosceles* spiders and against *Phoneutria* spiders, but there is little evidence of their efficacy.

Spider bites. Although many species of spider are venomous, relatively few pose a danger to man. Two main clinical syndromes are recognised: necrotic araneism, produced mainly by members of the genus *Loxosceles* which includes the brown recluse spider *L. reclusa*, and neurotoxic araneism produced by members of the genera *Latrodectus* (including the black widow and red-back spiders), *Phoneutria* (South American banana spiders), and *Atrax* (funnel-web spiders).

Necrotic araneism presents as local pain and erythema at the site of the bite, commonly developing into a necrotic lesion with a black eschar that sloughs after a few weeks, sometimes leaving an ulcer that heals gradually. The area affected can be extensive. Rarely, systemic symptoms including intravascular coagulation, haemolytic anaemia, respiratory distress, and renal failure, occur and may be life-threatening. Some therapies have been suggested, but conservative management is usually adequate with surgical repair of any persistent defects if necessary. Dapsone is reported to produce beneficial effects on healing. Treatment for systemic manifestations is supportive. Antisera are available in some countries.

Neurotoxic araneism may involve severe pain, headache, vomiting, tachycardia, hypertension, muscle spasms, and occasionally pulmonary oedema, and coma, depending upon the species. Antisera are available and reported to be more effective than those for necrotic araneism, but should be reserved for serious envenomation. Intravenous injection of calcium gluconate 10% has been suggested to relieve muscle spasm as an alternative to conventional muscle relaxants.

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2. Isbister GK, *et al.* Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003; **41:** 291–300.
3. Nimorakiotakis B, Winkel KD. The funnel web and common spider bites. *Aust Fam Physician* 2004; **33:** 244–51.
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5. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352:** 700–707.
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Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Aracmyn; Reclusmyn.

Staphylococcal Immunoglobulins

Profile

Staphylococcal immunoglobulins are under investigation for passive immunisation against infection with *Staphylococcus aureus*.

Two antistaphylococcal immunoglobulins, INH A-21 and *Altastaph*, have been used in Phase II and III studies for prevention of staphylococcal infections in very low birth-weight neonates, but a systematic review failed to find any significant reduction in the rate of bacterial infection.[1] Phase II and III studies for other antistaphylococcal immunoglobulins (Pagibaximab, Tefibazumab, and *Aurograb*) are underway.[1,2]

1. Shah PS, Kaufman DA. Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 15/12/09).
2. Deresinski S. Antistaphylococcal vaccines and immunoglobulins: current status and future prospects. *Drugs* 2006; **66:** 1797–1806.

Staphylococcal Vaccines

Vacunas estafilocócicas.

Profile

Staphylococcal vaccines have been developed for the prophylaxis of staphylococcal infections.

A vaccine containing *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A showed promise[1] in early studies in patients with end-stage renal disease who were receiving haemodialysis; however, later work failed to confirm benefit and its development was stopped.[1,2]

1. Shinefield H, *et al.* Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. *N Engl J Med* 2002; **346:** 491–6.
2. Deresinski S. Antistaphylococcal vaccines and immunoglobulins: current status and future prospects. *Drugs* 2006; **66:** 1797–1806.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Estafiloide†; *China*: Bo Ke Le Wei (博克乐威); *Cz.*: Polystafana†; Stafal†; *USA*: SPL.

Stone Fish Venom Antisera

Antídoto contra el veneno del pez piedra estuarino; Antisuero contra el veneno del pez piedra estuarino; Stone Fish Antivenins; Stone Fish Antivenoms.

Uses and Administration

An antiserum for use in the management of stings by the stone fish (*Synanceja trachynis*) is available in Australia. The antiserum is prepared from the serum of horses that have been immunised with the venom of the stone fish. Other symptomatic and supportive treatments are given in addition.

Stone fish venom antiserum may be given by intramuscular injection or, in more severe cases, by intravenous infusion. When given by intravenous infusion, it should be diluted 1 in 10 with an intravenous solution. The initial dose of stone fish antivenom given to both adults and children is dependent on the number of visible puncture sites: 1 to 2 puncture sites, 2000 units; 3 to 4 puncture sites, 4000 units; and 5 or more puncture sites, 6000 units. The initial dose may be repeated if necessary should symptoms persist.

References to the management of stone fish envenomation.

1. Sutherland SK. Stone fish bite. *BMJ* 1990; **300:** 679–80.
2. Lehmann DF, Hardy JC. Stonefish envenomation. *N Engl J Med* 1993; **329:** 510–11.
3. Brenneke F, Hatz C. Stonefish envenomation—a lucky outcome. *Travel Med Infect Dis* 2006; **4:** 281–5.
4. Grandcolas N, *et al.* Piqûres par poisson-pierre: une antalgie difficile, un risque notable de complications. *Presse Med* 2008; **37:** 395–400.
5. Prentice O, *et al.* Stonefish envenomation. *Am J Emerg Med* 2008; **26:** 972.e1–972.e2.
6. Ngo SY, *et al.* Stonefish envenomation presenting to a Singapore hospital. *Singapore Med J* 2009; **50:** 506–9.

Adverse Effects and Precautions

As for antisera in general, p. 2373.1.

Streptococcus Group B Vaccines

Vacunas contra estreptococos del grupo B.

Profile

Vaccines for active immunisation against group B streptococcal infections are being developed. Giving a vaccine to pregnant women to prevent neonatal infection has been proposed.

References.
1. Baker CJ, Edwards MS. Group B streptococcal conjugate vaccines. *Arch Dis Child* 2003; **88:** 375–8.

Tetanus Antitoxins

Antitoxinas del tétanos; Antitoxinas tetánicas.
ATC — J06AA02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tetanus Antitoxin for Human Use; Immunoserum Tetanicum ad Usum Humanum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Clostridium tetani*. It is obtained by fractionation from the serum of horses, or other mammals, that have been immunised against tetanus toxin. For prophylactic use, it has a potency of not less than 1000 international units/mL, and for therapeutic use not less than 3000 international units/mL. It should be stored at 2 degrees to 8 degrees, and not be allowed to freeze.

The BP 2014 states that Tet/Ser may be used on the label.

Profile

Tetanus antitoxins neutralise the toxin produced by *Clostridium tetani* and have been used to provide temporary passive immunity against tetanus, but tetanus immunoglobulins (below) are preferred. A test dose of tetanus antitoxin should always be given to identify those who might suffer hypersensitivity reactions.

Whenever a non-immune patient is seen because of injury, a course of active immunisation should be instituted (see Tetanus Vaccines, p. 2421.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Anti-Tet (ATS); *Philipp.*: Antitet; Tetanox; Toxigen.

Pharmacopoeial Preparations
Ph. Eur.: Tetanus Antitoxin for Human Use.

Tetanus Immunoglobulins

Inmunoglobulinas contra el tétanos.
ATC — J06BB02.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Tetanus Immunoglobulin; Immunoglobulinum Humanum Tetanicum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the toxin of *Clostridium tetani*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

USP 36: (Tetanus Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with tetanus vaccine. It contains not less than 50 units of tetanus antitoxin/mL. 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

Tetanus immunoglobulins are used for passive immunisation against tetanus.

The use of tetanus immunoglobulins is recommended in the UK and the USA as part of the management of tetanus-prone wounds in persons unimmunised or incompletely immunised against tetanus, in persons whose immunisation history is unknown, in those who have received the last dose of tetanus vaccine more than 10 years previously, and in patients with impaired immunity. Active immunisation with a tetanus vaccine (p. 2421.1) should also be started simultaneously, and antibacterials and symptomatic therapy given as appropriate (see p. 209.2 and p. 2029.2). The usual dose of tetanus immunoglobulin is 250 units by intramuscular injection but, if more than 24 hours have elapsed since the wound was sustained, or if there is a risk of heavy contamination, or after burns, 500 units should be given irrespective of the immunisation history.

Tetanus immunoglobulin is also used in the treatment of tetanus, a recommended dose being 150 units/kg in total, given intramuscularly into multiple sites.

A preparation suitable for intravenous use is available in some countries. It is given for the treatment of tetanus in a dose of 5000 to 10 000 units by intravenous infusion.

Adverse Effects and Precautions

As for immunoglobulins in general, p. 2373.2.

Interactions

As for immunoglobulins in general, p. 2373.2.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gammatet; Igantet; *IT* SD-T; Tetabulin; *Austria*: Tetabulin; Tetagam; *Belg.*: Tetabuline; *Braz.*: Tetanogamma; *Canad.*: Hypertet; *Chile*: Igantet; *Cz.*:

Tetabulin; *Fr.*: Gammatetanos; *Ger.*: Tetagam; Tetanobulin†; *Gr.*: Igantet; Tetagam-P; Tetanosson; Tetuman; *Hong Kong*: Hyper-Tet; Tetagam; *Hung.*: Tetig; *India*: Beats; Igantet; Tetagam-P; *Indon.*: Tetagam P; *Irl.*: Tetabulin; *Israel*: HyperTET; *Ital.*: Gamma-Tet P; Igantet; Tetabulin; Tetanus-Gamma; *Malaysia*: Igantet; Sero-Tet; *Mex.*: Tetanogamma; *Neth.*: Teta-Quin; *Philipp.*: BayTet†; IG Tetano†; Sero-Tet; Tetagam-P; Tetanea; *Pol.*: Tetabulin; *Port.*: Tetagam; *S.Afr.*: Tetagam; *Singapore*: Igantet; *Spain*: Gamma Antitetanos; Tetagamma P†; *Switz.*: Tetagam; *Thai.*: Tetagam; Tetanus Gamma; *Turk.*: Bay-Tet; Tetanea; Tetaquintetatus; Tetuman†; *USA*: BayTet†.

Pharmacopoeial Preparations

Ph. Eur.: Human Tetanus Immunoglobulin;
USP 36: Tetanus Immune Globulin.

Tetanus Vaccines

Vacunas del tétanos.
ATC — J07AM01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tetanus Vaccine (Adsorbed); Vaccinum Tetani Adsorbatum). It is prepared from tetanus formol toxoid adsorbed on a mineral carrier which may be hydrated aluminium phosphate or aluminium hydroxide. The resulting mixture is isotonic with blood. Suitable antimicrobial preservatives may be added. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type and these should not be added to the vaccine. It contains not less than 40 units 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 Tet may be used on the label.

The BP 2014 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

BP 2014: (Tetanus Vaccine). It is prepared from tetanus toxin produced by the growth of *Clostridium tetani*. The toxin is converted to tetanus formol toxoid by treatment with formaldehyde solution. It contains suitable non-phenolic antimicrobial preservatives. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Tet/Vac/FT may be used on the label.

The BP 2014 directs that when Tetanus Vaccine is prescribed or demanded and the form is not stated, Tetanus Vaccine (Adsorbed) may be dispensed or supplied.

Uses and Administration

Tetanus vaccines are used for active immunisation against tetanus.

For primary immunisation combined tetanus vaccines, usually diphtheria, tetanus, and pertussis vaccines (p. 2383.3) or diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenzae vaccines (p. 2385.3), are used. For discussion of immunisation schedules, see under Vaccines, p. 2373.3. In adults requiring primary immunisation combined vaccines such as diphtheria and tetanus vaccines (p. 2383.1) or diphtheria, tetanus, and poliomyelitis vaccines (p. 2386.2) are used.

In children who complete the primary course in infancy, reinforcing doses are given at school entry (about 4 to 6 years) and in adolescence using the recommended appropriate combined vaccines. In adults, a reinforcing dose is desirable 10 years later with a further dose after a further 10 years.

Tetanus vaccines should be part of wound management if primary immunisation is incomplete or boosters are not up-to-date. For tetanus-prone wounds, tetanus immunoglobulin (see p. 2420.3) may also be required. Tetanus vaccine and tetanus immunoglobulin may be given at the same time, but not at the same site. In the event of injury in non-immunised persons or if immunisation status is uncertain, the opportunity is usually taken to start a course of primary immunisation. Since this provides no immediate protection, prophylactic treatment with tetanus immunoglobulin is recommended for tetanus-prone wounds. Suitable antibacterial therapy may also be given (see p. 209.2).

References.
1. WHO. Tetanus vaccines: WHO position paper. *Wkly Epidem Rec* 2006; 75: 198–208. Also available at: http://www.who.int/immunization/wer8120ctetanus_May06_position_paper.pdf (accessed 30/05/10)

Neonatal tetanus. In 1989 WHO adopted a resolution to eliminate neonatal tetanus after estimates revealed that worldwide (but excluding China) it was the cause of 800 000 neonatal deaths each year, a figure representing about 50% of all such deaths in developing countries. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of the mother in late pregnancy. However, by mid-2000 there were 57 countries that had still not eliminated maternal and neonatal tetanus and WHO, UNICEF, and UNFPA agreed to set a target date of 2005 for elimination (defined as a rate of neonatal tetanus below 1 in 1000 live births at district level). However, by the end of 2007, 47 countries were still considered to have not achieved elimination.

Tetanus vaccine is given to all women of child-bearing age as part of WHO's Expanded Programme on Immunization. For pregnant women, 2 doses of vaccine should be given, the second dose at least 4 weeks after the first and at least 2 weeks before delivery; this may provide the newborn infant with about 80% protection against tetanus. For all women of child-bearing age, 3 doses of vaccine, with at least 4 weeks between the first two doses and 6 to 12 months between the second and third doses, provide 95 to 98% protection for at least 5 years. Fourth and fifth doses, each at least one year after the previous dose, prolong the immunity for 10 and 20 years respectively.

Reinforcing doses in adults. Although the current recommendation in the UK is that 5 doses of tetanus vaccine (as a 3-dose primary course in infancy and 2 reinforcing doses at pre-school and in adolescence) is sufficient to produce satisfactory long-term protection in most circumstances, there has been concern about immunity in the elderly, and in particular women. Routine primary immunisation against tetanus was introduced in the UK in 1961, so individuals born before that year would not have been immunised in infancy, and unless they had been in the armed forces, may never have received a full primary course. Unless there is a clear immunisation history immunity to tetanus may be difficult to assess. It is also recommended in the UK that travellers to areas where medical attention may not be accessible, and who had the last dose of vaccine more than 10 years previously, should receive a booster even if they have had 5 doses previously.

Studies in the USA,[1] Australia,[2] and Austria[3] have shown that at least half of healthy people over 50 years of age did not have adequate circulating tetanus antibodies. However, the level of circulating antibodies in the absence of an antigen challenge may not be an appropriate measure of the immune status. The low incidence of clinical tetanus in adults provides circumstantial evidence of an adequate inducible antibody response on exposure to tetanus despite a decline in antibody concentrations with increasing age.[4,5] Conversely, there have been reports of tetanus occurring despite high antibody concentrations.[6,7] There have been calls for the introduction of regular booster injections in adults,[3,7-9] as is standard practice in the USA or alternatively a single booster in late middle age[10,11] or giving a primary course to elderly persons who have never received one.[1]

1. Gergen PJ, *et al.* A population-based serologic survey of immunity to tetanus in the United States. *N Engl J Med* 1995; 332: 761–6.
2. Heath TC, *et al.* Tetanus immunity in an older Australian population. *Med J Aust* 1996; 164: 593–6.
3. Steger MM, *et al.* Vaccination against tetanus in the elderly: do recommended vaccination strategies give sufficient protection? *Lancet* 1996; 348: 762.
4. Bowie C. Tetanus toxoid for adults—too much of a good thing. *Lancet* 1996; 348: 1185–6.
5. Baily G. Are the elderly inadequately protected against tetanus? *Lancet* 1996; 348: 1389–90.
6. Passen EL, Andersen BR. Clinical tetanus despite a 'protective' level of toxin-neutralising antibody. *JAMA* 1986; 255: 1171–3.
7. Bowman C, *et al.* Tetanus toxoid for adults. *Lancet* 1996; 348: 1664.
8. Rethy LA, Rethy L. Can tetanus boosting be rejected? *Lancet* 1997; 349: 359–60.
9. Sehgal R. Tetanus toxoid for adults. *Lancet* 1997; 349: 573.
10. Balestra DJ, Littenberg B. Tetanus immunization in adults. *JAMA* 1994; 272: 1900.
11. Gardner P, LaForce FM. Protection against tetanus. *N Engl J Med* 1995; 333: 599.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local reactions, usually after the use of adsorbed vaccines, and mild systemic reactions may occur. The incidence and severity of reactions increases with the number of doses given.

Anaphylaxis and neurological reactions have been reported rarely.

Although vaccination is usually postponed in patients suffering from an acute febrile illness, tetanus vaccine should be given to such patients in the presence of a tetanus-prone wound.

With the exception of the first booster dose of tetanus vaccine (which is usually given before school entry and about 3 years after the primary course), further boosters should not generally be given at intervals of less than 10 years because of an increased risk of severe local reactions.

Effects on the nervous system. Neuropathies have been reported rarely with tetanus vaccination. Optic neuritis and myelitis occurred[1] in an 11-year-old girl after a routine booster dose. Corticosteroids and immunoglobulin were given, and both vision and muscle power were restored after 11 months. Acute transverse myelitis was reported[2] in a 50-year-old man who received a tetanus vaccine and immunoglobulin after an injury. Neurological deficits were unchanged after 1 month despite use of corticosteroids. Other causes could not be ruled out in either case. Brachial neuritis that developed in 2 infants after immunisation with diphtheria, tetanus, and pertussis vaccine was attributed to the tetanus component.[3]

1. Topaloglu H, *et al.* Optic neuritis and myelitis after booster tetanus toxoid vaccination. *Lancet* 1992; 339: 178–9.
2. Read SJ, *et al.* Acute transverse myelitis after tetanus toxoid vaccination. *Lancet* 1992; 339: 1111–12.
3. Hamati-Haddad A, Fenichel GM. Brachial neuritis following routine childhood immunization for diphtheria, tetanus, and pertussis (DTP): report of two cases and review of the literature. *Pediatrics* 1997; 99: 602–3.

GUILLAIN-BARRÉ SYNDROME. For a discussion on the relationship between tetanus-containing vaccines and Guillain-Barré syndrome, see Diphtheria and Tetanus Vaccines, p. 2383.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies 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 02/11/11)

Pregnancy. No connection has been found between use of tetanus vaccine during pregnancy and either congenital malformations[1] or spontaneous abortion.[2]

1. Silveira CM, *et al.* Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. *Bull WHO* 1995; 73: 605–8.
2. Cataindig N, *et al.* Tetanus toxoid and spontaneous abortions: is there epidemiological evidence of an association? *Lancet* 1996; 348: 1098–9.

Interactions

As for vaccines in general, p. 2375.3.

Tetanus immunoglobulins will neutralise tetanus toxoid and should not be injected into the same site or in the same syringe as a tetanus vaccine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tetanol; Tetavax; *Austral.*: Tet-Tox†; *Austria*: Tetanol; *Chile*: Tetavax; *Cz.*: Alteana; Tetanol; Tetavax; *Ger.*: Tetanol; *Gr.*: Anatoxal-Te-Berna; Tetanol; *Hong Kong*: Te Anatoxal†; Tetatox; Tetavax; *Hung.*: Tetanol; *India*: Bett; *Ital.*: Anatetall; Imovax Tetano; *Malaysia*: TT Vaccine; *Mex.*: Tetamyn†; Tetanol; Tetinox; *Norw.*: Tetavax; *NZ*: Te Anatoxal†; Tet-Tox; *Philipp.*: Anatetall; Imatet; T-Vac; Te Anatoxal†; Tet-vac; Tetavax; Tetliv; Tetox; *S.Afr.*: Tetavax; *Singapore*: Tetavax; *Spain*: Anatoxal Tedi; *Switz.*: Tetanol pur; *Thai.*: Anatetall; Bio-TT; Te Anatoxal†; Tetavax; TT Vaccine; *Turk.*: Anatetall†; Tetavax; *USA*: Te Anatoxal.

Pharmacopoeial Preparations

Ph. Eur.: Tetanus Vaccine (Adsorbed).

Tetanus and Influenza Vaccines

Vacunas del tétanos y la gripe.

Profile

Tetanus and influenza vaccines are available in some countries for active immunisation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Tetagrip†.

Tetanus and Poliomyelitis Vaccines

Vacunas del tétanos y la poliomielitis.

Profile

Tetanus and poliomyelitis (inactivated) vaccines have been used in some countries for active immunisation against tetanus and poliomyelitis.

Tick Venom Antisera

Antídoto contra las picaduras de garrapata; Antisuero contra el veneno de garrapata; Tick Antivenins; Tick Antivenoms.

Profile

An antiserum is available in Australia for treatment of the neurotoxic effects of envenomation by the tick *Ixodes*

holocyclus. The antiserum is prepared from the serum of dogs that have been immunised with tick venom.

Tick venom antiserum is given by slow intravenous infusion.

Tick-borne Encephalitis Immunoglobulins

Inmunoglobulinas de la encefalitis transmitida por garrapatas.
ATC — J06BB12.

Profile

Preparations containing antibodies against tick-borne encephalitis are available in some countries for passive immunisation against the disease.

Tick-borne Encephalitis Vaccines

Vacunas de la encefalitis transmitida por garrapatas.
ATC — J07BA01.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Tick-borne Encephalitis Vaccine (Inactivated); Vaccinum Encephalitidis Ixodibus Advectae Inactivatum). A liquid preparation of a suitable strain of tick-borne encephalitis virus grown in cultures of chick-embryo cells or other suitable cell cultures and inactivated by a suitable method. 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 Tic/enceph may be used on the label.

Uses and Administration

A vaccine is available in some countries for active immunisation against tick-borne viral encephalitis.

In the UK, vaccination against tick-borne encephalitis is recommended for those who anticipate prolonged exposure to the infective agent, for example persons visiting or working in the warm forested parts of Europe and Scandinavia. The vaccine is given by intramuscular injection in adult doses of 0.5 mL. The primary course consists of three doses, the second being given 4 to 12 weeks after the initial dose, and a third dose 5 to 12 months later. In children over 1 year of age and below 16 years of age, 3 doses of 0.25 mL of the junior formulation of the vaccine are given; the intervals between each dose are the same as for the adult schedule. To achieve rapid short-term protection in adults and children, the second dose may be given 2 weeks after the first dose. Booster doses for adults and children at continued risk should be given within 3 years of the last primary vaccination or booster dose.

References.

1. Demicheli V, *et al.* Vaccines for preventing tick-borne encephalitis. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2009 (accessed 18/12/09).

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Effects on the nervous system. Severe progressive sensorimotor spastic paralysis occurred in a 54-year-old man after a second booster dose of tick-borne encephalitis vaccine.[1] Partial recovery was noted after about 6 months.

1. Bohus M, *et al.* Myelitis after immunisation against tick-borne encephalitis. *Lancet* 1993; **342**: 239–40.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tick-borne encephalitis 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. *Austria*: Encepur; FSME-Immun; *Belg.*: FSME-Immun; *Canad.*: FSME-Immun; *China*: Sen Tai Bao (森泰保); Cz.: Encepur; FSME-Immun; *Denm.*: Encepur; TicoVac; *Fin.*: Encepur; TicoVac; *Fr.*: Encepur; TicoVac; *Ger.*: Encepur; FSME-Immun; *Gr.*: Encepur; *Hung.*: Encepur; FSME-Immun; *Irl.*: TicoVac; *Ital.*: TicoVac; *Neth.*: FSME-Immun; *Norw.*: TicoVac; *Pol.*: Encepur; FSME-Immun; *Port.*: FSME-Immun; *Rus.*: Encepur (Энцепур); Encevir (Энцевир); *Swed.*: Encepur; FSME-Immun; *Switz.*: Encepur; FSME-Immun; *UK*: TicoVac.

Pharmacopoeial Preparations

Ph. Eur.: Tick-borne Encephalitis Vaccine (Inactivated).

Trichomoniasis Vaccines

Vacunas de la tricomoniasis.

Profile

A trichomoniasis vaccine containing inactivated *Lactobacillus* spp. is available in some countries for the prophylaxis of recurrent vaginal trichomoniasis. The vaccine is reported to stimulate production of antibodies against the aberrant coccoid forms of the lactobacilli associated with trichomoniasis and also, by cross-reaction, against the trichomonads themselves.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Booster-Gynatren; Gynatren.

Tularaemia Vaccines

Vacunas de la tularemia.

Profile

A tularaemia vaccine prepared from a live attenuated strain of *Francisella tularensis* has been used for active immunisation against tularaemia in persons at high risk of contracting the disease.

References.

1. Titball R, Oyston P. A vaccine for tularaemia. *Expert Opin Biol Ther* 2003; **3**: 645–53.
2. Conlan JW. Vaccines against Francisella tularensis: past, present and future. *Expert Rev Vaccines* 2004; **3**: 307–14.
3. Oyston PC. Francisella tularensis vaccines. *Vaccine* 2009; **27** (suppl 4): D48–D51.
4. Pechous RD, *et al.* Working toward the future: insights into Francisella tularensis pathogenesis and vaccine development. *Microbiol Mol Biol Rev* 2009; **73**: 684–711.

Typhoid Vaccines

Vacunas de la fiebre tifoidea.
ATC — J07AP01; J07AP02; J07AP03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Typhoid Vaccine; Vaccinum Febris Typhoidi). A sterile suspension of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone, formaldehyde, or phenol, or by phenol and heat. The vaccine should be stored at 2 degrees to 8 degrees, and be protected from light.

The BP 2014 states that Typhoid may be used on the label.

Ph. Eur. 8: (Typhoid Vaccine, Freeze-dried; Vaccinum Febris Typhoidi Cryodesiccatum). A freeze-dried preparation of inactivated *Salmonella typhi* containing not less than 500 million and not more than 1000 million bacteria per dose which does not exceed 1 mL. It is prepared from a suitable strain of *S. typhi* such as Ty 2. The bacteria are inactivated by heat, or by treatment with acetone or formaldehyde. Phenol may not be used in the preparation. The vaccine should be stored at 2 degrees to 8 degrees, and be protected from light. It is reconstituted by the addition of suitable sterile liquid and should be used within 8 hours.

The BP 2014 states that Typhoid may be used on the label.

Ph. Eur. 8: (Typhoid Vaccine (Live, Oral, Strain Ty 21a); Vaccinum Febris Typhoidis Vivum Perorale (Stirpe Ty 21a)). A freeze-dried preparation of live *S. typhi* strain Ty 21a grown in a suitable medium. It contains not less than 2×10^9 bacteria per dose. It should be stored at 2 degrees to 8 degrees, and be protected from light.

The BP 2014 states that Typhoid(live,oral) may be used on the label.

Ph. Eur. 8: (Typhoid Polysaccharide Vaccine; Vaccinum Febris Typhoidis Polysaccharidicum). A preparation of purified Vi capsular polysaccharide obtained from *S. typhi* Ty2 strain or some other suitable strain that has the capacity to produce Vi polysaccharide. It contains 25 micrograms of polysaccharide per dose. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Typhoid may be used on the label.

Uses and Administration

Typhoid vaccines are used for active immunisation against typhoid fever. As with many vaccines, the efficacy of typhoid vaccine is not complete and the importance of maintaining attention to hygiene should be emphasised to those travelling to endemic areas.

Typhoid vaccination is advised for laboratory workers handling specimens which may contain typhoid organisms and for persons travelling to areas where typhoid fever is endemic. In the UK, vaccination of contacts of a known typhoid carrier is not recommended; in the USA such persons are advised to receive the vaccine. Typhoid vaccine is not useful in controlling outbreaks of the disease in non-endemic areas.

In the UK, two vaccines are used: a capsular polysaccharide vaccine for parenteral use, and a live oral vaccine.

The capsular polysaccharide typhoid vaccine contains 25 micrograms of the Vi polysaccharide antigen per dose. A single dose of 0.5 mL is given by deep subcutaneous or intramuscular injection. Booster doses may be given every 3 years to those who remain at risk. The response in children under 18 months of age may be suboptimal, and the decision to vaccinate will be governed by the risk of exposure to infection.

The live oral typhoid vaccine contains an attenuated strain of *Salmonella typhi*, Ty 21a, and is given as enteric-coated capsules containing not less than 2×10^9 bacteria per dose. A primary immunisation schedule of one capsule every other day for 3 doses is given.

In the USA, the Vi capsular polysaccharide vaccine and the live oral Ty 21a vaccine are available. The capsular polysaccharide vaccine is given intramuscularly similarly to that in the UK, with a booster dose suggested every 2 years. For the oral vaccine, 4 doses on alternate days are recommended for both primary immunisation and boosters, which are given every 5 years if exposure continues.

In areas where typhoid is endemic WHO advises that immunisation should be considered as part of the routine schedules: either the Vi capsular polysaccharide vaccine or the Ty 21a live oral vaccine should be given to schoolchildren over the age of 2 years. Immunisation of the whole community should also be considered during an outbreak of typhoid; if this is not possible, persons aged 2 to 19 years should be the target group.

References.

1. WHO. Typhoid vaccines: WHO position paper. *Wkly Epidem Rec* 2008; **83**: 49–59. Also available at: http://www.who.int/wer/2008/wer8306.pdf (accessed 30/06/10)

Immunisation for travellers. In most developed countries where typhoid is not endemic, the main use for typhoid vaccine is for non-immune travellers visiting endemic areas. The highest incidence of the disease is associated with travel to the Indian subcontinent and parts of tropical South America, although immunisation is also recommended for travellers to lower risk areas of Africa, Asia, and south-east Europe. By far the most important form of protection against gastrointestinal infection is strict attention to personal, food, and water hygiene, although in practice this advice is often difficult to follow.[1]

None of the vaccines used has been 100% effective in preventing disease. Their efficacy has generally been assessed in field studies in the populations of endemic areas. Such populations acquire a degree of natural immunity due to continued exposure and it may not be possible to equate protection rates in these populations to non-immune travellers. The live oral vaccine has been shown to confer a useful degree of immunity in field studies but the dose used may have been insufficient to protect non-immune individuals. The degree of immunity induced may be increased by the use of higher inocula or liquid preparations. In addition, compliance with dosing and storage requirements may further limit the efficacy of this dosage form.

Large field studies have verified the efficacy of the capsular polysaccharide vaccine but its efficacy has not been assessed in non-immune populations. However, it does have the advantage of being given as a single dose.

Whole-cell vaccines are generally no longer used because they are frequently associated with adverse effects.

1. WHO. *The diagnosis, treatment and prevention of typhoid fever.* Geneva: WHO, 2003. Also available at: http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf (accessed 20/02/06)

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Oral live typhoid and parenteral polysaccharide vaccines have been associated with fewer adverse effects than parenteral killed typhoid vaccines and have replaced them in many countries.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies typhoid vaccines (live oral and polysaccharide) 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 02/11/11)

Interactions

As for vaccines in general, p. 2375.3.

Conflicting advice has been issued about the use of live oral typhoid vaccines with antibacterials or antimalarials (particularly mefloquine or proguanil). WHO has stated that all these drugs should be stopped from 3 days before until 3 days after receiving the Ty 21a live oral vaccine. The UK licensed product information advises a separation of 3 days for antibacterials, 12 hours for mefloquine (although licensed product information for mefloquine recommends at least 3 days), and 3 days for other antimalarials (but the fixed-dose combination of atovaquone and proguanil may be given with the vaccine). The US product information has indicated that mefloquine (and chloroquine) can be given with the vaccine but that proguanil should only be taken 10 days after the vaccine. US licensed product information for mefloquine, however, advises waiting at least 3 days after vaccination is completed before starting mefloquine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Typhim Vi; Vivotif; *Austral.*: Typherix; Typhim Vi; Vivotif; *Austria*: Typherix; Typhim Vi; Vivotif; *Belg.*: Typherix; Typhim Vi; Vivotif; *Canad.*: Typherix; Typhim Vi; Vivotif; *Chile*: Typhim Vi; Vivotif; *China*: Typhim Vi (达易Vi); *Cz.*: Typherix; Typhim Vi; *Denm.*: Typherix; Typhim Vi; Vivotif; *Fin.*: Typherix; Typhim Vi; Vivotif; *Fr.*: Typherix; Typhim Vi; *Ger.*: Typherix; Typhim Vi; Typhoral L; *Gr.*: Typherix; Vivotif; *Hong Kong*: Typherix†; Typhim Vi; Vivotif; *Hung.*: Typherix; Typhim Vi; *India*: Biovac Typhoid; Typhim Vi; Typhoral; Vactyph; *Indon.*: Typherix; Typhim Vi; Vivotif; *Irl.*: Typherix; Typhim Vi; *Israel*: Typherix; Typhim Vi; *Ital.*: Typherix; Typhim Vi; Vivotif; *Malaysia*: Typherix; Typhim Vi; Vivotif; *Neth.*: Typherix; Typhim Vi; Vivotif; *Norw.*: Typherix; Typhim Vi; Vivotif; *NZ*: Typh-Vax; Typherix; Typhim Vi; Vivotif; *Philipp.*: Typherix; Typhim Vi; Vivotif; *Pol.*: Typhim Vi; *Port.*: Typherix; Typhim Vi; *S.Afr.*: Typherix; Typhim Vi; *Singapore*: Typherix; Typhim Vi; Vivotif; *Spain*: Typherix; Typhim Vi; Vivotif; *Swed.*: Typherix; Typhim Vi; Vivotif; *Switz.*: Vivotif; *Thai.*: Typbar; Typhim Vi; Vivotif†; *Turk.*: Typhim†; *UK*: Typherix; Typhim Vi; Vivotif; *USA*: Typhim Vi; Vivotif.

Pharmacopoeial Preparations

Ph. Eur.: Freeze-dried Typhoid Vaccine; Typhoid Polysaccharide Vaccine; Typhoid Vaccine (Live, Oral, Strain Ty 21a); Typhoid Vaccine.

Vaccinia Immunoglobulins

Inmunoglobulinas contra el virus de la vacuna.

ATC — J06BB07.

UNII — 7UB4J759TD (human vaccinia virus immunoglobulin).

Pharmacopoeias. Many pharmacopoeias, including *US*, have monographs.

USP 36: (Vaccinia Immune Globulin). A sterile solution of globulins derived from the plasma of adult human donors who have been immunised with vaccinia virus (smallpox vaccine). It contains 15 to 18% of protein, of which not less than 90% is gamma globulin. It contains glycine as a stabilising agent, and a suitable antimicrobial agent. It should be stored at 2 degrees to 8 degrees.

Profile

Vaccinia immunoglobulins have been used intramuscularly for the treatment of clinical complications of smallpox vaccination. They are not effective for postviral encephalitis. An intravenous vaccinia immunoglobulin is available in the USA.

References.

1. Hopkins RJ, *et al.* Safety and pharmacokinetic evaluation of intravenous vaccinia immune globulin in healthy volunteers. *Clin Infect Dis* 2004; 39: 759–66.
2. Hopkins RJ, Lane JM. Clinical efficacy of intramuscular vaccinia immune globulin: a literature review. *Clin Infect Dis* 2004; 39: 819–26.

Preparations

Pharmacopoeial Preparations

USP 36: Vaccinia Immune Globulin.

Varicella-Zoster Immunoglobulins

Inmunoglobulinas contra el herpesvirus 3 humano; Inmunoglobulinas contra el virus de la varicela zóster.

ATC — J06BB03.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii) and *US*, have monographs.

Ph. Eur. 8: (Human Varicella Immunoglobulin; Immunoglobulinum Humanum Varicellae). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having specific antibodies against *Herpesvirus varicellae*. Normal immunoglobulin may be added. It contains not less than 100 international units/mL. The liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under inert gas.

Ph. Eur. 8: (Human Varicella Immunoglobulin for Intravenous Administration; Immunoglobulinum Humanum Varicellae ad Usum Intravenosum). A sterile liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from selected donors having antibodies against human herpesvirus 3 (varicella-zoster virus 1). Human normal immunoglobulin for intravenous administration may be added. It contains not less than 25 international units/mL. Storage requirements are similar to those for Human Varicella Immunoglobulin, except that the freeze-dried preparation is stored at a temperature not exceeding 25 degrees.

USP 36: (Varicella-Zoster Immune Globulin). A sterile solution of globulins derived from the plasma of adult donors selected for high titres of varicella-zoster antibodies. It contains 15 to 18% of globulins, of which not less than 99% is immunoglobulin G with traces of immunoglobulin A and immunoglobulin M. It contains glycine as a stabilising agent and thiomersal as a preservative. It contains not less than 125 units of specific antibody in not more than 2.5 mL of solution. It should be stored at 2 degrees to 8 degrees.

Uses and Administration

Varicella-zoster immunoglobulins are used for passive immunisation against varicella (chickenpox) in susceptible persons considered to be at high risk of developing varicella-associated complications after exposure to varicella or herpes zoster (shingles).

In the UK, varicella-zoster immunoglobulins are recommended for individuals who are at high risk of severe varicella and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include immunosuppressed patients, neonates including those whose mothers develop chickenpox (but not herpes zoster) in the period 7 days before to 7 days after delivery, and pregnant women. Varicella-zoster immunoglobulin does not prevent infection when given after exposure but may modify the course of disease. Treatment with antivirals may be necessary in severe disease (see p. 956.2).

The doses, given by deep intramuscular injection, of the varicella-zoster immunoglobulin available in the UK are: 250 mg for children up to 5 years of age; 500 mg for those aged 6 to 10 years; 750 mg for those aged 11 to 14 years; and 1 g for all those 15 years of age or older. A further dose is required if a second exposure occurs more than 3 weeks later. Varicella-zoster immunoglobulin should be given as soon as possible and not later than 10 days after exposure. Preparations of normal immunoglobulin for intravenous use may be used to provide an immediate source of antibody.

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.*: Varitect; *Austria*: Varitect; *Canad.*: VariZIG; *Ger.*: Varicellon; Varitect; *Gr.*: Varitect; *Hong Kong*: Varitect†; *Irl.*: Varitect†; *Israel*: Varitect; *Ital.*: Varitect; *Neth.*: VariQuin; *Pol.*: Varitect†; *Port.*: Varitect†; *S.Afr.*: Vazigam; *Singapore*: Varitect†; *Switz.*: Varitect; *Thai.*: Varitect†; *Turk.*: Immunozig†; Varitect; *USA*: Varizig.

Pharmacopoeial Preparations

Ph. Eur.: Human Varicella Immunoglobulin for Intravenous Administration; Human Varicella Immunoglobulin;

USP 36: Varicella-Zoster Immune Globulin.

Varicella-Zoster Vaccines

Vacunas de la varicela zóster; Ветряночные Вакцины.

ATC — J07BK01.

Pharmacopoeias. Many pharmacopoeias have monographs including *Eur.* (see p. vii).

Ph. Eur. 8: (Shingles (Herpes Zoster) Vaccine (Live); Vaccinum Zonae Vivum). A freeze-dried preparation of a suitable attenuated strain of human herpesvirus 3 grown in cultures of human diploid cells. The culture medium may contain suitable antibiotics at the smallest effective concentration. It is reconstituted immediately before use to give a clear or slightly opalescent liquid, almost white suspension, or pale yellow liquid that may be coloured owing to the presence of a pH indicator. It is intended for use in adults. The dried vaccine should be stored at 2 degrees to 8 degrees. Protect from light.

Ph. Eur. 8: (Varicella Vaccine (Live); Vaccinum Varicellae Vivum). A freeze-dried preparation of a suitable attenuated strain of human herpesvirus 3 grown in cultures of human diploid cells. The culture medium may contain suitable antibiotics at the smallest effective concentration. It is reconstituted immediately before use to give a clear liquid that may be coloured owing to the presence of a pH indicator; it may contain a stabiliser. The dried vaccine should be stored at 2 degrees to 8 degrees. Protect from light.

The BP 2014 states that Var(Live) may be used on the label.

Uses and Administration

Live attenuated varicella-zoster vaccines may be used for active immunisation against varicella (chickenpox) and herpes zoster (shingles).

In the UK, vaccination against varicella is recommended only for persons considered to be at high risk of contracting the infection or highly susceptible to any complications it might cause; such patients include susceptible healthcare workers, and healthy contacts of immunocompromised patients when continuing close contact is unavoidable. Children from 1 year of age and adults may be given two doses (of 0.5 mL each), either intramuscularly or subcutaneously (depending on the product used); doses must be given 4 to 8 weeks apart.

In the USA, a 2-dose vaccination regimen against varicella is recommended as part of the primary immunisation schedule of infants and children (see under Vaccines, p. 2373.3). The first dose of 0.5 mL is given subcutaneously to children aged 12 to 15 months and the second dose at 4 to 6 years of age. Routine vaccination is also recommended for persons over the age of 7 years without evidence of immunity; two doses are given at an interval of at least 3 months in those aged 7 to 12 years and at least 28 days apart in those 13 years of age and older. Those who only received 1 dose should receive a second, catch-up dose.

In the USA, a high potency vaccine (containing a minimum of 19 400 plaque-forming units) against herpes zoster is recommended for persons 60 years of age and older. A single dose of 0.65 mL is given subcutaneously. In the UK, use of this vaccine is recommended for adults aged 70 years old.

A combination vaccine of measles, mumps, rubella, and varicella (MMRV) is available in the USA for use in children aged 12 months to 12 years.

References.

1. WHO. Varicella vaccines: WHO position paper. *Wkly Epidem Rec* 1998; 73: 241–48. Also available at: http://www.who.int/immunization/wer7332varicella_Aug98_position_paper.pdf (accessed 30/06/10)
2. Oxman MN. Zoster vaccine: current status and future prospects. *Clin Infect Dis* 2010; 51: 197–213.

Results of studies of varicella-zoster vaccines for active immunisation against chickenpox in healthy and leukaemic children have been largely favourable. Protective efficacy in healthy children appears to be over 90%. In healthy adolescents and adults, adding a second dose 4 or 8 weeks after the first increased seroconversion rates from about 70 to 80% to 97% or better.[1] A protective efficacy of about 85% has been reported in leukaemic children given one dose of varicella-zoster vaccine[2,3] and interruption of chemotherapy for vaccination does not appear necessary in terms of immunogenicity of the vaccine.[2,4]

The **duration of immunity** after a 1-dose regimen for active immunisation against chickenpox is also under debate; despite at least 70 to 90% efficacy, some consider that a single dose does not provide sufficient herd immunity levels to prevent outbreaks, especially in school settings.[5,6] Initial studies show that the immunity induced by natural infection with wild type virus is superior to that induced by the vaccine. In one study,[3] antibodies were absent in about one-quarter of all vaccinees (both leukaemic children and

The symbol † denotes a preparation no longer actively marketed

healthy adults) 1 year after a second dose of vaccine, but were still present after up to 6 years in all those who had breakthrough varicella infection.

However, immunity to varicella-zoster is complex, depending not only on circulating antibody but also on cellular immunity and secretory antibody. Thus, although a person may become seronegative after vaccination, protection from varicella may remain, albeit partial.[2] Both humoral and cell mediated immunity have been shown to persist for up to 20 years after vaccination.[7] Leukaemic children seen up to 6 years after immunisation have continued to be well protected[2] and varicella in previously-vaccinated persons is usually mild.[5,6]

Surveillance data collected from 11 356 children in the USA between 1995 and 2004 found that annual rates of breakthrough varicella increased significantly with time. Children aged 8 to 12 years at the onset of disease who had been vaccinated 5 years or more previously were 2.6 times more likely to have moderate or severe breakthrough varicella than those vaccinated less than 5 years previously.[8] The efficacy of a 2-dose vaccination regimen (doses given 3 months apart) was assessed in 2216 children over a period of 9 to 10 years.[9] Children vaccinated with the 2-dose regimen were 3.3 times less likely to develop varicella more than 42 days after vaccination than those who had received a single dose. During the 10-year follow-up period most breakthrough cases occurred in years 2 to 5, for both treatment regimens. No breakthrough cases were reported in years 7 to 10 for those who received the 2-dose regimen, while 10 cases were reported for those who received the 1-dose regimen. Since June 2007 the US Advisory Committee on Immunization Practices (ACIP) has recommended that children between the ages of 4 and 6 years receive a second dose of varicella vaccine.[6]

A systematic review suggests that varicella-zoster vaccine may prevent or modify varicella if given to children within 3 days of exposure to the infection.[10] It may be useful as an adjunct to varicella-zoster immunoglobulin. The treatment of varicella-zoster infections with antivirals is discussed on p. 956.2.

One concern of varicella-zoster vaccination has been the possibility of an **increased risk of herpes zoster** (shingles) in immunised children. Although herpes zoster has been reported in vaccinated persons, a study involving 346 leukaemic children and 84 matched controls concluded that the incidence of herpes zoster following varicella-zoster vaccine was no greater than that following natural varicella infection.[11] The study did suggest that the risk of herpes zoster may be lowered by vaccination but this must be confirmed by long-term follow-up. Postmarketing surveys[12] of almost 90 000 vaccine recipients also showed a low incidence of herpes zoster. The vaccine strain of varicella-zoster virus is transmissible, particularly from vaccinees who develop a rash. There is no evidence of reversion to virulence of the vaccine strain with secondary transmission.

Another concern is that vaccination of children could result in more severe infections in later life after immunity has waned. However, studies have shown that in general varicella is less severe in previously immunised than in non-immunised patients.[13,14]

The risk of zoster increases with age reflecting the waning of the specific cell-mediated immunity to the virus. Thus, the use of a high-potency varicella-zoster vaccine has been investigated in elderly subjects.[15,16] In a randomised, double-blind, placebo-controlled study in over 38 000 subjects aged 60 years or more the vaccine reduced the burden of illness due to herpes zoster by 61.1% and the incidence of herpes zoster and of postherpetic neuralgia by 51.3% and 66.5% respectively.[17] A high-potency varicella-zoster vaccine is recommended by some authorities for all people 60 years of age and older,[18,19] including those who have already had an episode of shingles.[18] The efficacy of the varicella-zoster vaccine in preventing further infections in such patients has not been shown in clinical studies,[20] although immunogenicity of this vaccine 4 weeks after vaccination has been shown.[21]

1. Kuter BJ, *et al.* Safety, tolerability, and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy adolescents and adults. *Vaccine* 1995; 13: 967 72.
2. Gershon AA, *et al.* Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. *N Engl J Med* 1989; 320: 892–7.
3. Gershon AA, *et al.* Live attenuated varicella vaccine: protection in healthy adults compared with leukemic children. *J Infect Dis* 1990; 161: 661–6.
4. Arbeter AM, *et al.* Immunization of children with acute lymphoblastic leukemia with live attenuated varicella vaccine without complete suspension of chemotherapy. *Pediatrics* 1990; 85: 338–44.
5. Lopez AS, *et al.* One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics* 2006; 117: 2253–4. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/6/e1070 (accessed 06/07/07)
6. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; 56 (RR-4): 1–40. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5604.pdf (accessed 06/07/07)
7. Asano Y, *et al.* Experience and reason: twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. *Pediatrics* 1994; 94: 524–6.
8. Chaves SS, *et al.* Loss of vaccine-induced immunity to varicella over time. *N Engl J Med* 2007; 356: 1121–9.
9. Kuter B, *et al.* Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J* 2004; 23: 132–7.
10. Macartney K, McIntyre P. Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 18/12/09).
11. Lawrence R, *et al.* The risk of zoster after varicella vaccination in children with leukemia. *N Engl J Med* 1988; 318: 543–8.
12. Black S, *et al.* Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; 18: 1041–6.
13. Watson BM, *et al.* Modified chickenpox in children immunized with the Oka/Merck varicella vaccine. *Pediatrics* 1993; 91: 17–22.
14. Bernstein HH, *et al.* Clinical survey of natural varicella compared with breakthrough varicella after immunization with live attenuated Oka/Merck varicella vaccine. *Pediatrics* 1993; 92: 833–7.
15. Sanford M, Keating GM. Zoster vaccine (Zostavax): a review of its use in preventing herpes zoster and postherpetic neuralgia in older adults. *Drugs Aging* 2010; 27: 159–76.
16. Keating GM. Shingles (herpes zoster) vaccine (Zostavax(†)): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged ≥ 50 years. *Drugs* 2013; 73: 1227–44.
17. Oxman MN, *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; 352: 2271–84.
18. CDC. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008; 57: 1–30. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm (accessed 12/02/10)
19. Public Health England. Shingles vaccine special edition (issued September 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239832/vaccine_update_12_9_v3.pdf (accessed 24/10/13)
20. Adams EN, *et al.* Herpes zoster and vaccination: a clinical review. *Am J Health-Syst Pharm* 2010; 67: 724–7.
21. Mills R, *et al.* Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine* 2010; 28: 4204–9.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Varicella vaccines for active immunisation against chickenpox are generally well tolerated. Rashes may occur at the injection site and generalised varicella-like rashes elsewhere have been reported. The vaccine strain of virus can become latent, which could result in late development of zoster infections, but the incidence of herpes zoster is lower after vaccination than in an unvaccinated population. Breakthrough cases of chickenpox have been reported after single- and 2-dose vaccination regimens, but were in most cases milder. The incidence of breakthrough varicella is markedly lower after the 2-dose regimen.

High potency varicella vaccines licensed for active immunisation against herpes zoster (shingles) should not be used for active immunisation against varicella (chickenpox). Such vaccines are contra-indicated in patients with a history of anaphylactic reactions to neomycin or gelatin.

Transmission of the vaccine strain of the virus may occur rarely between those who developed a varicella-like rash after vaccination and susceptible contacts. The vaccines are contra-indicated in patients with severe immunosuppression and those with active untreated tuberculosis should not be vaccinated.

General references.

1. Black S, *et al.* Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* 1999; 18: 1041–6.
2. Simberkoff MS, *et al.* Safety of herpes zoster vaccine in the Shingles Prevention Study: a randomized trial. *Ann Intern Med* 2010; 152: 545–54.

Effects on the eye. See Effects on the Nervous System, below.

Effects on the nervous system. Twenty months after immunisation with varicella-zoster virus vaccine a 3½-year-old immunocompetent child developed herpes zoster opthalmicus and encephalitis; molecular analysis confirmed the vaccine strain as the causative agent. The child made a full recovery with no neurologic sequelae after treatment with intravenous and topical aciclovir.[1]

1. Choullaras G, *et al.* Vaccine-associated herpes zoster ophthalmicus and encephalitis in an immunocompetent child. *Pediatrics* 2010; 125: 807. Full version: http://www.pediatrics.org/cgi/content/full/125/4/e969 (accessed 10/11/10)

Pregnancy. Normally occurring varicella zoster infection may cause fetal harm, therefore as a precautionary measure, vaccination of pregnant women against varicella is generally contra-indicated; advice is also given to avoid pregnancy for 3 months after the last dose of vaccine. However, surveillance of women inadvertently vaccinated during pregnancy has not identified any increased risk, either in terms of congenital varicella or for congenital abnormalities.

It should also be noted that the vaccine strain of varicella-zoster virus is transmissible, particularly from vaccinees who develop a rash.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Varicela Biken; Varilrix; *Austral.*: Varilrix; Varivax; Zostavax; *Austria*: Varilrix; Varivax; Zostavax; *Belg.*: Provarivax; Varilrix; *Braz.*: Vacina Contra A Varicela (Virus Atenuado); Vacina Contra Varicela; *Canad.*: Varilrix; Varivax; Zostavax; *Chile*: Biken; Varilrix; *China*: Huiliwei (惠立维); Varilrix (威可禄); Wei Zhi Wei (维稚维); Weiruile (维瑞乐); *Cz.*: Varilrix; Zostavax; *Denm.*: Varilrix; *Fin.*: Varilrix; *Fr.*: Varilrix; Varivax; *Ger.*: Varilrix; Varivax; Zostavax†; *Gr.*: Varilrix; Varirix; Varivax; *Hong Kong*: Okavax; Varilrix; Varivax; *Hung.*: Varilrix; *India*: Okavax; Varilrix; Varipox†; *Indon.*: Okavax; Varilrix; *Irl.*: Varivax; Zostavax; *Israel*: Varilrix; Zostavax; *Ital.*: Varilrix; Varivax; *Malaysia*: Okavax; Varilrix; *Mex.*: Okavax; Varilrix; Varivax; *Neth.*: Provarivax; Zostavax; *Norw.*: Varilrix; *NZ*: Varilrix; Varivax; Zostavax; *Philipp.*: Okavax; V-Z Vax; Varilrix; *Pol.*: Varilrix; Zostavax; *Port.*: Varilrix; Varivax; Zostavax; *Rus.*: Okavax (Окавакс); Varilrix (Варилрикс); *S.Afr.*: Varilrix; *Singapore*: Okavax; Varilrix; *Spain*: Varilrix; Varivax; *Swed.*: Varilrix; *Switz.*: Varilrix; Varivax; Zostavax; *Thai.*: Okavax; Varilrix; *Turk.*: Okavax; Varilrix; *UK*: Varilrix; Varivax; Zostavax; *Ukr.*: Varilrix (Варилрикс); *USA*: Varivax; Zostavax; *Venez.*: Varilrix.

Pharmacopoeial Preparations

Ph. Eur.: Shingles (Herpes Zoster) Vaccine (Live); Varicella Vaccine (Live).

Yellow Fever Vaccines

Vacunas de la fiebre amarilla.

ATC — J07BL01.

UNII — 4G601DAM77 (yellow fever virus antigen); PY4EET359T (yellow fever virus live antigen).

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p. vii), have monographs.

Ph. Eur. 8: (Yellow Fever Vaccine (Live); Vaccinum Febris Flavae Vivum). A freeze-dried preparation of yellow fever virus derived from the 17D strain and grown in fertilised hen eggs. It is reconstituted immediately before use. It should be stored at 2 degrees to 8 degrees and be protected from light.

The BP 2014 states that Yel(live) may be used on the label.

Uses and Administration

Yellow fever vaccines are used for active immunisation against yellow fever. Immunity is usually established within about 10 days of administration and persists for many years. Only one dose is required for immunisation and is given by deep subcutaneous injection; the dose (0.5 mL) is the volume containing at least 1000 mouse LD_{50} units.

In the UK, immunisation against yellow fever is recommended for laboratory workers handling infected material, for persons travelling through or living in areas of infection, and for travellers entering countries which require an International Certificate of Vaccination. The immunity produced may last for life although officially an International Certificate of Vaccination against yellow fever is valid only for 10 years starting 10 days after the primary immunisation and only if the vaccine used has been approved by WHO and given at a designated centre.

Vaccination under 9 months of age is not generally recommended (see Adverse Effects and Precautions, p. 2425.1).

General references.

1. Barrett ADT. Yellow fever vaccines. *Biologicals* 1997; 25: 17–25.
2. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; 78: 349–59. Also available at: http://www.who.int/wer/2003/en/wer7840.pdf (accessed 30/06/10)
3. Barnett ED. Yellow fever: epidemiology and prevention. *Clin Infect Dis* 2007; 44: 850–6.
4. Barrett AD, Teuwen DE. Yellow fever vaccine - how does it work and why do rare cases of serious adverse events take place? *Curr Opin Immunol* 2009; 21: 308–13.
5. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59 (RR-7): 1–27. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5907.pdf (accessed 02/09/10)

Immunisation schedules. The 17D (Rockefeller) yellow fever vaccine is now the only yellow fever vaccine produced.[1,2] The quantity available in the world has been limited and its relatively short half-life does not permit the accumulation of large stocks. The demand for the vaccine is also somewhat irregular, being suddenly high during epidemics and low during inter-epidemic periods.

In Africa and in South America two different strategies for yellow fever immunisation have been followed.[1,2] Firstly, an emergency immunisation programme takes place once an outbreak has begun, in an attempt to limit the spread of infection by immunising all persons in the focus, regardless of their former immune status. One disadvantage is that immunity does not appear until 7 days after immunisation and deaths may be expected to occur in the interim period. Secondly, a routine mass immunisation

programme for yellow fever is aimed at immunising in advance all populations considered to be at risk. Yellow fever vaccine is included in the WHO Expanded Programme on Immunization; there are obvious logistic advantages in giving it at the age of 9 months at the same time as measles vaccine. In rural areas of the endemic zone that are considered at high risk, the minimum age for routine immunisation may be lowered to 6 months (see Vaccine-associated Neurotropic Disease, below).

1. WHO. *Prevention and control of yellow fever in Africa*. Geneva: WHO, 1986.
2. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; 78: 349–60.

Immunisation for travellers. A guide entitled *International Travel and Health* is published annually by WHO. Information is provided concerning the countries in Africa and South America where yellow fever is endemic and also countries requiring a traveller to hold a valid vaccination certificate. For some further details, see p. 2374.3.

Adverse Effects and Precautions

As for vaccines in general, p. 2375.1.

Local and general reactions are not common after vaccination for yellow fever. Very rarely encephalitis has occurred, generally in infants under 9 months of age. Therefore, yellow fever vaccine is not usually given to infants under 9 months (but see Vaccine-associated Neurotropic Disease, below).

There are as yet limited data on the safety of yellow fever vaccine in HIV-positive individuals. In the UK, it is recommended that specialist advice should be sought regarding the use of yellow fever vaccine in such individuals. WHO notes that the vaccine has been given to HIV-positive individuals who are symptomatic. For further information on the use of yellow fever vaccine in HIV-infected individuals, see below.

Breast feeding. In the USA, the Advisory Committee on Immunization Practices[1] recommends that yellow fever vaccination of nursing mothers be avoided, except when travel to high-risk yellow fever-endemic areas cannot be avoided or postponed.

1. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; 51 (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

HIV Infection. There is a high prevalence of HIV infection in many countries where yellow fever is endemic, but immunogenicity and safety data on the use of the 17D yellow fever vaccine in HIV-infected individuals are limited. A study[1] of 102 HIV-infected individuals (with mainly mild to moderate immunodeficiency) vaccinated with the 17D yellow fever vaccine reported no serious adverse events after vaccination, but noted that the immunogenicity of the vaccine was impaired in HIV-infected individuals compared with those not infected with HIV. HIV-infected individuals with undetectable HIV RNA levels and higher CD4+ T lymphocyte counts had a better response to the vaccine. Furthermore, the authors considered that a booster vaccination every 10 years for HIV-infected individuals was probably insufficient and suggested that determination of neutralisation titre or revaccination should be considered after 2 to 5 years in the event of potential exposure.

1. Veit O, *et al.* Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* 2009; 48: 659–66.

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

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

Pregnancy. Although yellow fever vaccine has been given to women during pregnancy without producing adverse effects in the infants,[1] fetal infection has been reported.[2] In the USA recommendations[3] therefore advise that the safety of yellow fever vaccination during pregnancy has not been established and the vaccine should only be given to pregnant women if travel to an endemic area is unavoidable and if an increased risk of exposure exists. Infants born to these women should be monitored closely for evidence of congenital infection or other adverse effects.

1. Nasidi A, *et al.* Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans R Soc Trop Med Hyg* 1993; 87: 337–9.
2. Tsai TF, *et al.* Congenital yellow fever virus infection after immunization in pregnancy. *J Infect Dis* 1993; 168: 1520–3.
3. CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR* 2002; 51 (RR-17): 1–11. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5117.pdf (accessed 25/05/06)

Vaccine-associated neurotropic disease. Yellow fever vaccine has been associated with rare reports of encephalitis, now termed vaccine-associated neurotropic disease (YEL-AND). WHO has stated[1] that, since 1945, there have been at least 26 cases of proven or probable YEL-AND of which 16 occurred in infants aged less than 6 months. Of the 26 cases, 24 recovered without further complications and there were 2 fatalities.[1] Vaccine virus recovered from one of the fatalities, a 3-year-old child, revealed that mutation had occurred in the envelope gene of the virus, but it is unknown whether similar mutations occurred in the other cases. The other fatality occurred in an immunocompromised adult with HIV infection. As a precaution against possible encephalitis, infants less than 9 months of age are not generally immunised, although it may be advisable to immunise at 6 to 8 months of age during epidemics.

A laboratory-confirmed case of yellow fever vaccine-associated neurologic disease occurred in an infant due to the transmission of yellow fever vaccine virus through breast milk. The infant recovered completely with antibacterial and antiviral treatment for meningoencephalitis and follow-up of the infant showed normal neurodevelopment and growth through age 6 months.[2]

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; 78: 349–59.
2. CDC. Transmission of yellow fever vaccine virus through breast-feeding - Brazil, 2009. *MMWR* 2010; 59: 130–2.

Vaccine-associated viscerotropic disease. Yellow fever vaccine has been associated with rare reports of multiple organ failure, now termed yellow fever vaccine-associated viscerotropic disease (YEL-AVD). WHO has stated[1] that, between 1996 and 2001, there were 7 recorded cases (6 fatal) of YEL-AVD of which 2 occurred in Brazil,[2] 4 in the USA,[3] and one in Australia.[4] A further case, also leading to fatality, was reported to have occurred in Spain in 2004,[5] and 5 cases, 4 fatal, in 2007 in Peru.[6] It has been suggested that the most likely explanation is an idiosyncratic host susceptibility to the 17D vaccine strain rather than a reversion of the vaccine strain to a wild-type strain.[5] There is also some evidence to suggest that the risk of YEL-AVD is greater in patients aged over 60 years.[7]

1. WHO. Yellow fever vaccine: WHO position paper. *Wkly Epidem Rec* 2003; 78: 349–59.
2. Vasconcelos PFC, *et al.* Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. *Lancet* 2001; 358: 91–7. Corrections. *ibid.*; 336. *ibid.*; 1018.
3. Chan RC, *et al.* Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. *Lancet* 2001; 358: 121–2.
4. Martin M, *et al.* Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. *Lancet* 2001; 358: 98–104.
5. Agencia Española del Medicamentos y Productos Sanitarios. A death associated with yellow fever vaccination reported in Spain. Available at: http://www.eurosurveillance.org/ew/2004/041104.asp (accessed 25/08/05)
6. Whittembury A, *et al.* Viscerotropic disease following yellow fever vaccination in Peru. *Vaccine* 2009; 27: 5974–81.
7. Khromava AY, *et al.* Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005; 23: 3265–63.

Interactions

As for vaccines in general, p. 2375.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Stamaril; *Austral.*: Stamaril†; *Austria*: Stamaril; *Belg.*: Stamaril; *Canad.*: YF-Vax; *Chile*: Stamaril; *Cz.*: Stamaril; *Denm.*: Stamaril; *Fin.*: Arilvax†; Stamaril; *Fr.*: Stamaril; *Ger.*: Stamaril; *Hong Kong*: Stamaril†; *Hung.*: Stamaril; *Irl.*: Stamaril; *Israel*: Arilvax†; Stamaril; *Ital.*: Stamaril; *Malaysia*: Stamaril; *Neth.*: Arilvax†; Stamaril; *Norw.*: Stamaril; *NZ*: Stamaril; *Pol.*: Stamaril; *Port.*: Stamaril; *S.Afr.*: Arilvax†; Stamaril; *Singapore*: Stamaril; *Spain*: Stamaril; *Swed.*: Stamaril; *Switz.*: Stamaril; *Turk.*: Stamaril†; *UK*: Arilvax; Stamaril; *USA*: YF-Vax.

Pharmacopoeial Preparations

Ph. Eur.: Yellow Fever Vaccine (Live).

The symbol † denotes a preparation no longer actively marketed

Miscellaneous Drugs and Other Substances

This chapter includes some drugs not easily classified, herbal medicines, new drugs whose place in therapy is not yet clear, and drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

Abrus

Abrus Seed; Bejuco de peonia; Indian Liquorice; Jequirity Bean; Jumble Beads; Prayer Beads; Regaliz americano; Rosary Beans; Semillas del regaliz americano.

Profile

Abrus consists of the seeds of *Abrus precatorius* (Leguminosae), one of whose constituents is abrin. Abrin, which is closely related to ricin, is considered responsible for the toxic effects of the seeds. Children have died from eating one or more seeds. Toxicity may be less likely to occur if the seeds are swallowed whole, than if they are chewed, because of the hard seed coat. Toxic effects may occur within a few hours or may be delayed for several days after ingestion. Signs and symptoms of abrin poisoning are similar to those described for ricin, p. 2604.2.

Abrus has been used as an oral contraceptive in herbal medicine.

Homoeopathy

Abrus has been used in homoeopathic medicines under the following names: Jequirity.

References.

1. Aslam M, Shaw JMH. Abrus in Asian medicine. *Pharm J* 1998; 261: 822–4.
2. Fernando C. Poisoning due to Abrus precatorius (jequirity bean). *Anaesthesia* 2001; 56: 1178–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Enkasari; Ika Sariawan; *Rus.*: Travisil (Трависил); *Ukr.*: Travisil (Трависил).

Homoeopathic Preparations. *Austral.*: Sedatif†; *Canad.*: Sedatil; *Cz.*: Sedatif PC; *Fr.*: Sedatif PC; *Hung.*: Sedatif; *Neth.*: Sedatif PC; *Port.*: Sedatif PC; *Rus.*: Homeostres (Гомеострес); *Switz.*: Sedatif PC; *Ukr.*: Sedatif PC (Седатив ПЦ).

Absinthium

Absinthe; Absinthii herba; Absintio; Ajenjo; Ajorizo; Artemisa; Assenzio; Fehér üröm fű; Hierba santa; Incienso de Andalucía; Karčiųjų kiečių žolė; Losna; Mali, Koiruoho; Malört; Pelin; Pelyňková nať; Wermutkraut; Wormwood; Ziele piołunu; Полынь Горькая.

CAS — 546-80-5 (α-thujone); 471-15-8 (β-thujone).
*ATC Herb — HA03AW5004 (*Artemisia absinthium*: herb); HA05AW5002 (*Artemisia absinthium*: herb); HA09WA5002 (*Artemisia absinthium*: herb); HP02WA5001 (*Artemisia absinthium*: herb).*
UNII — F84709P2XV.

NOTE. The name Hierba Santa (yerba santa) has been applied to many plants including species of the genus *Eriodictyon* (p. 1665.2).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of absinthium:

Green Fairy; Green Goddess; La Fée Verte.

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

Ph. Eur. 8: (Wormwood). The leaves or flowering tops, or a mixture of these dried, whole or cut organs of wormwood, *Artemisia absinthium*. It contains not less than 2 mL/kg of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Absinthium has been used as a bitter. It is also used in small quantities as a flavour in alcoholic beverages, although it is considered in some countries to be unsafe for use in foods, beverages, or drugs. Habitual use or large doses cause absinthism, which is characterised by restlessness, vomiting, vertigo, tremors, and convulsions. Thujone, related to camphor, is the major constituent of the essential oil derived from absinthium.

Absinthium has been investigated in the treatment of inflammatory bowel disease.

Homoeopathy

Absinthium has been used in homoeopathic medicines under the following names: Artemisia absinthium; Artemisia absinthium ex herba siccata; Absinth.

References.

1. Welsbord SD, *et al.* Poison on line—acute renal failure caused by oil of wormwood purchased through the Internet. *N Engl J Med* 1997; 337: 825–7.
2. Skyles AJ, Sweet BV. Wormwood. *Am J Health-Syst Pharm* 2004; 61: 239–42.
3. Omer B, *et al.* Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. *Phytomedicine* 2007; 14: 87–95.
4. Krebs S, *et al.* Wormwood (*Artemisia absinthium*) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease—a controlled clinical trial. *Phytomedicine* 2010; 17: 305–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Nat Pelynku Praveho†.

Multi-ingredient Preparations. *Austral.*: Wormwood Complex; *Austria*: Abdomilon N; Magentee St Severin; Mariazeller; Pervivo; Sigman-Haustropfen; *Braz.*: Camomila; *Canad.*: Gallexier†; Para-Gard; *Cz.*: Original Schwedenbitter; Zaludecni Cajova Smes; *Fr.*: Tisane Hepatique de Hoerdt†; *Ger.*: Abdomilon N; Amara-Tropfen; Floradix Multipretten N; Gallemolan forte†; Gallexier; Gastritol; Pascopankreat; ventri-loges N†; *Hung.*: Bitmer; *Pol.*: Artemisol; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; *Rus.*: Gastroguttal (Гастроуттал); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Amara†; *Switz.*: Baume Zeller; Gouttes Amara; Kernosan Heidelberger Poudre; Metabol; Pommade au Baume; Wala Elixir amer; *Ukr.*: Gastritol (Гастритол); Maraslavin (Мараславин).

Homoeopathic Preparations. *Canad.*: Amaratopfen†; Formula ES 211; *Fr.*: Carominthe; Yucca Complexe No 110; *Ger.*: Cefatropin N†; Gastritis Complex; K 1000; Magen-Darm-Entoxin N; Magen-Darmtropfen N; Ventrigutt M; *Rus.*: Nux Vom-Plus (Нукс Вом-Плюс); *UK*: Nausyn.

Acedoben *(pINN)*

Acedobén; Acédobène; Acedobenum; Ацедобен.

p-Acetamidobenzoic acid.

$C_9H_9NO_3$=179.2
CAS — 556-08-1.
UNII — 04Z20NMK31.

Profile

Acedoben is a component of inosine pranobex (p. 988.3), and has been given orally as the potassium salt in the treatment of skin disorders. Acedoben and its sodium salt have been applied topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Hongosan†.

Aceglutamide *(rINN)*

Aceglutamida; Acéglutamide; Aceglutamidum; Ацеглутамид.

N^2-Acetyl-L-glutamine; 2-Acetylamino-L-glutaramic acid.

$C_7H_{12}N_2O_4$=188.2
CAS — 2490-97-3.
UNII — 01J18G9G97.

Profile

Aceglutamide has been given in an attempt to improve memory and concentration. Aceglutamide aluminium (p. 1814.3) is used as an antacid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Li Su (爱立苏); Ai Lu Na (艾鲁那); Ai Sen Ao (艾森奥); Ao Li Xi (奥立喜); Ao Yi Ning (奥怡宁); Dan Nuo (丹诺); De Yi Fen (德益芬); Di Yi (迪依); Fu Ao (扶奥); Gan Fen (干芬); Han Xue (涵雪); He Di Xin (赫迪新); Hui Le (慧乐); Jian Yi (健意); Jin Jie Shu (劲杰纾); Jun Da Ke (均达柯); Kang Da Li Cun (康达利存); Kang Pa Si (康帕斯); Li Shu Kang (力枢康); Long Ge Xian (隆格先); Long Sheng Tai (龙胜泰); Lu Si Kai (路斯开); Meng Qing (梦清); Miao Si Ning (妙司宁); Nuo An Ping (诺安平); Nuoyi (诺依); Qi Shi (奇势); Rui Ke An (瑞可安); Sa Ni Ka (萨尼卡); Sai Pu Li Er (赛普利尔); ShengDi (胜迪); Shuai Ning (帅宁); Su Yi Ning (苏忆宁); Tian Xing (天醒); Tu Er (土尔); Wan Xin Neng (万欣能); Xun Bo (讯博); Yi Ming (忆明); Yi Pei (一培); YiQing (意清); YiXin (宜信); You Ni Sheng (尤尼生); Yun Ke Shu (云可舒).

Multi-ingredient Preparations. *Chile*: Cebrocal; *Ital.*: Acutil Fosforo; *Mex.*: Italviron.

Acemannan *(USAN, rINN)*

Acemanán; Acémannan; Acemannanum; Polymanoacetate; Ацеманнан.

CAS — 110042-95-0.
UNII — UZ29E6L2X8.

Profile

Acemannan is a highly acetylated, polydispersed, linear mannan obtained from the mucilage of *Aloe vera* (*A. barbadensis*). It has immunomodulating properties and is an ingredient of topical wound dressing products including those formulated for the oral mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Carrasyn; DiaB Gel; Oral Wound Rinse; RadiaGel; SaliCept; Ultrex.

Acetic Acid

Acide acétique; Ácido acético; Ácido etanóico; Ácido etílico; Ácido metanocarboxílico; Acidum Aceticum; Acto rūgštis; Asetik Asit;Ättiksyra; E260; Ecetsav; Eisessig (glacial acetic acid); Essigsäure; Etanoico; Ethanoic Acid; Etikkahappo; Kwas octowy; Kyselina octová.

$C_2H_4O_2$=60.05
CAS — 64-19-7.
ATC — G01AD02; S02AA10.
ATC Vet — QG01AD02; QS02AA10.
UNII — Q40Q9N063P.

NOTE. The nomenclature of acetic acid often leads to confusion over whether concentrations are expressed as percentages of glacial acetic acid ($C_2H_4O_2$) or of a diluted form. In *Martindale*, the percentage figures given against acetic acid represent the amount of $C_2H_4O_2$.

Pharmacopoeias. Glacial acetic acid is included in *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Solutions containing about 30 to 37% are included in *Br.* (33%), *Chin.* (36 to 37%), *Int.*, *Jpn* (30 to 32%), and *Swiss* (30%). Also in *USNF* (36 to 37%).

Dilute acetic acid (6%) is included in *Br.* and *Int.* Also in *USNF*.

Ph. Eur. 8: (Acetic Acid, Glacial; Acidum Aceticum Glaciale). A crystalline mass or a clear colourless volatile liquid. F.p. not lower than 14.8 degrees. Miscible with water, with alcohol, and with dichloromethane. Store in airtight containers.

BP 2014: (Acetic Acid (33 per cent)). It contains 32.5 to 33.5% w/w of $C_2H_4O_2$. It is a clear colourless liquid with a pungent odour. Miscible with water, with alcohol, and with glycerol.

BP 2014: (Acetic Acid (6 per cent)). It contains 5.7 to 6.3% w/w of $C_2H_4O_2$. It is prepared by diluting Acetic Acid (33 per cent).

USP 36: (Glacial Acetic Acid). A clear colourless liquid with a pungent characteristic odour. B.p. about 118 degrees.

Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 31: (Acetic Acid). It contains 36 to 37% w/v of $C_2H_4O_2$. It is a clear colourless liquid with a strong characteristic odour. Miscible with water, with alcohol, and with glycerol. Store in airtight containers.

USNF 31: (Diluted Acetic Acid). It contains 5.7 to 6.3% w/v of $C_2H_4O_2$. It is prepared by diluting Acetic Acid. Store in airtight containers.

Uses and Administration

Glacial acetic acid has been used as an escharotic. Diluted forms have been used as an antibacterial (it is reported to be effective against *Haemophilus* and *Pseudomonas* spp.), antifungal, and antiprotozoal in vaginal gels and douches, irrigations, topical preparations for the skin and nails, and in ear drops. Diluted forms have also been used as an expectorant, an astringent lotion, and as treatments for warts (p. 1689.3), callosities, and for certain jellyfish stings (see below). Solutions have also been used to soften ear wax (p. 1836.3) and in the treatment of otitis externa (p. 195.1). Visual inspection of the uterine cervix with acetic acid (VIA) is being investigated as a screening method for cervical cancer, particularly where facilities for cytological methods may be limited.

A solution containing 4% w/v $C_2H_4O_2$ is known as artificial vinegar or non-brewed condiment. Vinegar is a product of fermentation.

Jellyfish sting. Vinegar or acetic acid 3 to 10% is applied to box jellyfish stings to inactivate any fragments of adherent tentacle (see p. 2397.1). Acetic acid solutions have been reported to be useful in stings by related species[1] although they may produce further discharge of venom in some jellyfish.[2]

1. Fenner PJ, *et al.* "Morbakka", another cubomedusan. *Med J Aust* 1985; 143: 550–5.
2. Fenner PJ, Fitzpatrick PP. Experiments with the nematocysts of Cyanea capillata. *Med J Aust* 1986; 145: 174.

Wounds and burns. Infection of wounds (p. 1690.1) and burns (p. 1683.1) with *Pseudomonas aeruginosa* may delay healing. Acetic acid has been used, in concentrations of up to 5%, to eradicate these infections.[1]

1. Milner SM. Acetic acid to treat Pseudomonas aeruginosa in superficial wounds and burns. *Lancet* 1992; 340: 61.

Adverse Effects and Treatment

Local or topical application of acetic acid preparations may produce stinging or burning. Ingestion of glacial acetic acid can produce similar adverse effects to those of hydrochloric acid (p. 2529.1), which may be treated similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cutinova; Hexa-Defital Crema Enjuague; Otopreven; Pelo Libre Protectora; *Austral.*: Summer's Eve Douche; *Fr.*: Para Lentes†; *Ger.*: Liberanit†; *Gr.*: Instaret; *UK*: BarCalm; Meltus Baby; *USA*: Feminique; Massengill Disposable; Summer's Eve Disposable; *Venez.*: Duvagin; Fem Ducha; Gynovit.

Multi-ingredient Preparations. *Arg.*: Aglio†; Callicida; Detebencil Nit; Puera Bicho†; Hexa-Defital Plus; Microsona Otica; Uze Active; *Austral.*: Aqua Ear; Ear Clear for Swimmers Ear; *Belg.*: Aporil; *Braz.*: A Curitybina; Lacto Vagin; *Canad.*: Acid Concentrate; Haemosol H†; Naturalyte H; Viron Wart Lotion; *Chile*: Concentrado Acido; *China*: Solcoderm (恩可得); *Fr.*: Anticor†; Dialysol Acide†; Nitrol†; Ysol 206†; *Ger.*: AdaptaCide PAA-C; Gehwol Huhneraugen-Tinktur; Solco-Derman; *Gr.*: Otocort; *Hong Kong*: Baby Cough with Antihistamine†; Solcoderm†; *Hung.*: Strand; *India*: Otek-O; Perfocyn†; *Irl.*: Phytex†; *Ital.*: Cue Soluzione Otologica; Oleo Calcarea; *NZ*: VoSoL; *Pol.*: Acifungin; Solcogyn; *Rus.*: Bubil (Бубил)†; Solcoderm (Солкодерм); Solcovagin (Солковагин); *Spain*: Callicida Cor Pik†; Callicida Rojo†; Keranin†; Nitroina; Quocin; *Switz.*: Solcoderm; Solcogyn; Waruzol; *Thai.*: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; *Turk.*: Dilan†; Rendializat Sodyum; SH-206; Tuba; *UK*: Ellimans; Goddards Embrocation; Phytex; Potters Gees Linctus; Sanderson's Throat Specific; *Ukr.*: Solcoderm (Солкодерм); Solcovagin (Солковагин); *USA*: AABP; Acetasol HC; Acetasol; Acid Jelly†; Borofair Otic†; Burow's; Fem pH; Klout; Otic Domeboro; Otic Edge†; Star-Otic; VoSoL HC; *Venez.*: Kayivis; Saxacid.

Pharmacopoeial Preparations
BP 2014: Strong Ammonium Acetate Solution;
USP 36: Acetic Acid Irrigation; Acetic Acid Otic Solution; Hydrocortisone and Acetic Acid Otic Solution.

Acetohydroxamic Acid *(USAN, rINN)*

Acetohidroxámico, ácido; *N*-Acetyl Hydroxyacetamide; Acide Acétohydroxamique; Ácido acetohidroxámico; Acidum Acetohydroxamicum; AHA; Ацетогидроксамовая Кислота.
$C_2H_5NO_2$=75.07.
CAS — 546-88-3.
ATC — G04BX03.
ATC Vet — QG04BX03.
UNII — 4RZ82L2GY5.

Pharmacopoeias. In *US*.

USP 36: (Acetohydroxamic Acid). White, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform. Store in airtight containers at a temperature between 8 degrees and 15 degrees.

Uses and Administration

Acetohydroxamic acid inhibits bacterial urease and thus decreases urinary ammonia concentration and alkalinity. It is used as an adjunct in the treatment of chronic urinary-tract infections (p. 213.1). It has also been used in the prophylaxis of struvite renal calculi (p. 2350.3), although the benefits have not been clearly established.

Acetohydroxamic acid is given orally in a usual dose of 250 mg three or four times daily. The total dose should not exceed 1.5 g daily. For doses in children and in patients with renal impairment, see below.

Administration in children. Children with chronic recalcitrant urea-splitting urinary infection have been given acetohydroxamic acid orally in doses of 10 mg/kg daily in 2 or 3 divided doses for periods of up to 1 year. However close monitoring should be carried out since dosage and dose intervals have not been established in clinical studies.

Administration in renal impairment. Acetohydroxamic acid should not be given to patients with serum-creatinine concentrations in excess of about 220 micromoles/litre. If the concentration is between 160 and 220 micromoles/litre, the maximum daily dose given orally should be 1 g and the dosing interval should be extended to every 12 hours.

Adverse Effects and Precautions

Phlebitis, thromboembolism, haemolytic anaemia, and iron-deficiency anaemia have occurred. Bone-marrow depression has been reported in *animal* studies. Other adverse effects include headache, gastrointestinal disturbances, alopecia, rash (particularly after ingestion of alcohol), trembling, and mental symptoms including anxiety and depression. Blood counts and renal function should be monitored regularly during treatment. Patients with acute renal failure should not be given acetohydroxamic acid.

Pregnancy. Studies in *animals* indicate that acetohydroxamic acid is teratogenic.

Interactions

Acetohydroxamic acid chelates iron given orally, resulting in reduced absorption of both. Ingestion with alcohol may precipitate a rash.

Pharmacokinetics

Acetohydroxamic acid is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 1 hour. The plasma half-life is reported to be up to 10 hours, but may be longer in patients with impaired renal function. Acetohydroxamic acid is partially metabolised to acetamide, which is inactive; up to about two-thirds of a dose may be excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Uronefrex; *USA*: Lithostat.

Pharmacopoeial Preparations
USP 36: Acetohydroxamic Acid Tablets.

Acetylleucine *(rINN)*

Acetileucina; Acétylleucine; Acetylleucinum; RP-7542; Ацетиллейцин.
N-Acetyl-DL-leucine.
$C_8H_{15}NO_3$=173.2
CAS — 99-15-0.
ATC — N07CA04.
ATC Vet — QN07CA04.
UNII — K76S41V71X.

Profile

Acetylleucine has been used in the treatment of vertigo (p. 612.3) in usual oral doses of up to 2 g daily, in divided doses, or 1 g daily by intravenous injection. Higher doses have occasionally been used.

References.
1. Ferber-Viart C, *et al.* Effects of acetyl-DL-leucine in vestibular patients: a clinical study following neurotomy and labyrinthectomy. *Audiol Neurotol* 2009; 14: 17–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Tanganil.

Acexamic Acid *(BAN, rINN)*

Acexámico, ácido; Acide Acexamique; Ácido acexámico; Acidum Acexamicum; CY-153; Epsilon Acetamidocaproic Acid; Ацексамовая Кислота.
6-Acetamidohexanoic acid.
$C_8H_{15}NO_3$=173.2
CAS — 57-08-9 (acexamic acid); 70020-71-2 (zinc acexamate).
UNII — 7K4BO7D3R.

Pharmacopoeias. *Eur.* (see p. vii) includes Zinc Acexamate.

Profile

Acexamic acid is related structurally to the antifibrinolytic agent aminocaproic acid (p. 1131.3). Acexamic acid, usually as the calcium or sodium salt, has been used topically or systemically to promote the healing of ulcers and various other skin lesions. Zinc acexamate has been given for peptic ulcer disease.

References.
1. Reis AM, *et al.* Allergic contact dermatitis to acexamic acid. *Contact Dermatitis* 2008; 58: 241–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Plastenan; Restaurene; *China*: An Yi (安易); Wei Ke Xin (卫可欣); *Fr.*: Plastenan; *Mex.*: Recoveron; *Spain*: Copinal.

Multi-ingredient Preparations. *Arg.*: Bagoderm; Cicatrizol; Lisoderma; Plastenan con Neomicina; *Mex.*: Dermatolona; Recoveron N; Recoveron NC.

Achillea

Achillée millefeuille; Aquilea; Cickafarkfű; Cientoenrama; Kraujažolių žolė; Milenrama; Milfoil; Milhojas; Millefolii Herba; Rölleka; Schafgarbe; Schafgarbenkraut; Siankärsämö; Řebříčková nať; Yarrow; Ziele krwawnika; Тысячелистник Обыкновенный.
CAS — 8022-07-9 (yarrow root oil).
ATC Herb — HA03AW5001 (Achillea millefollium: herb); HA09WA5001 (Achillea millefolium: herb); HA05AW5001 (Achillea millefolium: herb); HC05AW5001 (Achillea millefolium: herb); HA03WX5001 (Achillea millefolium: herb); HG02WA5001 (Achillea millefolium: herb); HR05YA5001 (Achillea millefolium: herb); HM01AW5001 (Achillea millefolium: herb); HN02BG5001 (Achillea millefolium: herb).
UNII — 2FXJ6SW4PK.

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

Ph. Eur. 8: (Yarrow). The whole or cut, dried flowering tops of yarrow, *Achillea millefolium*. It contains not less than 2 mL/kg of essential oil and not less than 0.02% of proazulenes, expressed as chamazulene ($C_{14}H_{16}$=184.3), both calculated with reference to the dried drug. Protect from light.

Profile

Achillea has been used in herbal medicine. It has been stated to have diaphoretic, anti-inflammatory, and other miscellaneous properties. It has been reported to cause contact dermatitis.

Yarrow root oil is used in aromatherapy.

Homoeopathy

Achillea has been used in homoeopathic medicines under the following names: Achillea millefolium; Millefolium; Achillea ex herba; Millef.

References.
1. Anonymous. Final report on the safety assessment of yarrow (Achillea millefolium) extract. *Int J Toxicol* 2001; 20 (suppl 2): 79–84.
2. Benedek B, Kopp B. Achillea millefolium L. s.l. revisited: recent findings confirm the traditional use. *Wien Med Wochenschr* 2007; 157: 312–14.
3. Nemeth E, Bernath J. Biological activities of yarrow species (*Achillea* spp.). *Curr Pharm Des* 2008; 14: 3151–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Nat Rebricku†; Rebrickovy Caj, Rebrickova Nat†; *Mex.*: Blancaler.

Multi-ingredient Preparations. *Austral.*: DiaCo; Flavons†; Masculine Herbal Complex; *Austria*: Abfuhrtee St Severin; Amersan; Gallen- und Lebertee St Severin; Mariazeller; Menodoron; *Canad.*: Cystoforce†; Floradix Kindervital†; Honey Herb Cough Drops†; Natraway Sport 1 & 2†; Natraway Sport 3†; Original Herb Cough Drops†; *Cz.*: Amersan; Cicaderma; Projimava; Species Urologicae Planta; Zaludecni Cajova Smes; *Fr.*: Afra†; Colitisane†; Dexsil Articulations; Gonaxine; Tisane Hepatique de Hoerdt†; Tisane Provencale no 5†; *Ger.*: Alasenn; Amara-Tropfen; Floradix Multipretten N; Gallexier; Hevert Stoffwechsel-Tee N†; Imupret; Menodoron; Sedovent†; *Hung.*: Gallexier; Gastrosol; Hemorid; Hemorid; Majvedo es Detoxikalo; Menofit; Mensesyl; Salus Multipretten; Szent Lukacs; Urogin; Uroherb; *India*: Bonnisan; Geriforte; Geriforte; Hepaliv; Liv 52; *Ital.*: Bulboshap†; Forticrin; Lik-Gel†; Lozione Same Urto; Pik Gel; *Malaysia*: Bonnisan; *Pol.*: Amarosal; Artecholin†; Artecholwex†; Cholavisol; Dyspepsin; Enterosol; Gastrobonisol; Hemorol; Liv 52; Nefrobonisol; Nervosan†; Reumosol; Salviasept; Sanofil; *Port.*: Cicaderma; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); Evalar (Эвалар); Fitantis (Фитантис); GeKaTon (Жекатон); Kliophyt (Клиофит); Laxantis Species No 1 (Слабительный Сбор 1); Liv 52 (Лив 52); Liv 52 (Лив 52); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Phytohepatol No 2 (Фитогепатол 2); Polygemostat (Полигемостат); Proctophytol (Проктофитол); Rotocan (Ротокан); Tonsilgon N (Тонзилгон Н); *S.Afr.*: Amara†; Clairo†; Menodoron†; *Singapore*: Disco; Liv 52; Liv 52; *Swed.*: Multipretten; *Switz.*: Baume Zeller; Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Kernosan Heidelberger Poudre; Liv 52; Menodoron; Pommade au Baume; Tisane hepatique et biliaire; Tisane pour l'estomac; Venaphyt N; *UK*: Catarrh-eeze; Rheumatic Pain Remedy; Spotner; Tabritis; Wellwoman; *Ukr.*: Ambovit (Амбовит); Clotrex (Клотрекс); Imupret (Имупрет); Liv 52 (Лив 52); Tonsilgon N (Тонзилгон)†.

Homoeopathic Preparations. *Austral.*: Echine†; *Austria*: Traumeel; *Canad.*: Amaratopfen†; Cicaderma†; Traumeel; *Chile*: Variplex; *Cz.*: Traumeel; *Fr.*: Arnica Complexe no 1; Cicaderma; Diacure; Millefolium Complexe No 7†; *Ger.*: Heweven Complex; Infihepan; Regenaplex Haut W; Traumeel S; Venokatt; *Hung.*: Traumeel; *Neth.*: Achilite; Apo-STOM; Cystilite; Traumeel H; Traumeel S; *Rus.*: Cicaderma (Цикалерма); Traumeel S (Траумель С); *S.Afr.*: Achillea Comp†; Chamomilla/Millefolium Comp†; Traumeel S; *Switz.*: Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 59b; Traumeel; *UK*: Laxadoron; Menodoron; *Ukr.*: Traumeel S (Траумель С); *USA*: Traumeel; *Venez.*: Traumeel.

Acid Alpha Glucosidase

Acid Maltase; Alfa Glucosidasa; Amyloglucosidase; EC 3.2.1.3; Glucan 1,4-α-Glucosidase; α-Glucosidasa; Lysosomal α-glucosidase; Альфа-глюкозидаза.
CAS — 9032-08-0.

Alglucosidase Alfa *(BAN, USAN, rINN)*

Alglucosidasa alfa; Alglucosidasum Alfa; rhGAA; Альглюкозидаза Альфа.
CAS — 420784-05-0.
ATC — A16AB07.
ATC Vet — QA16AB07.
UNII — DTI67O9503.

NOTE. The name Pompase has been used as a trade mark for alglucosidase alfa.

Uses and Administration

Alglucosidase alfa is a recombinant form of human acid alpha glucosidase given as enzyme replacement therapy for the treatment of Pompe disease (see below). It is given intravenously using an infusion pump in doses of 20 mg/kg once every 2 weeks. The total volume of fluid, which is determined by the patient's body-weight, should be infused over about 4 hours. The infusion rate should be increased gradually: the initial rate should not exceed 1 mg/kg per hour; once the patient can tolerate this rate, it may be increased every 30 minutes by 2 mg/kg per hour with monitoring of vital signs before each increase; the maximum infusion rate is 7 mg/kg per hour.

Administration in children. Licensed product information mentions that there is no evidence for special consideration when alglucosidase alfa is used in children or adolescents for the treatment of Pompe disease and the *BNFC* notes that the usual adult dose (see above) may be given to neonates as well as infants and older children.

Pompe disease. Pompe disease (glycogen storage disease type II; glycogenosis type II; acid maltase deficiency) is a rare fatal autosomal recessive disorder caused by a deficiency of acid α-glucosidase, which cleaves α-1,4- and α-1,6-glucosidic linkages in lysosomal glycogen to liberate glucose. Glycogen accumulation results in progressive myopathy, especially of the respiratory and skeletal muscles, and the heart. Infantile-onset Pompe disease is rapidly progressive leading to cardiopulmonary failure in the first year of life. In juvenile and adult-onset forms of Pompe disease glycogen accumulation is limited mainly to the skeletal muscles and is more slowly progressive producing muscle weakness and varying degrees of respiratory weakness; a small proportion of patients may also have some cardiac involvement. Pompe disease is a multisystem disorder and extensive supportive treatment is required. Alglucosidase alfa is a recombinant form of human acid alpha glucosidase given as enzyme replacement therapy for Pompe disease with greatest benefit seen following treatment at an early stage of infantile-onset disease whereas evidence of efficacy in late-onset disease is limited.

References.

1. Amalfitano A, *et al.* Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. *Genet Med* 2001; 3: 132–8.
2. Van den Hout JM, *et al.* Enzyme therapy for Pompe disease with recombinant human alpha-glucosidase from rabbit milk. *J Inherit Metab Dis* 2001; 24: 266–74.
3. Kishnani PS, Howell RR. Pompe disease in infants and children. *J Pediatr* 2004; 144 (suppl): S35–S43.
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6. van der Beek NA, *et al.* Pompe disease (glycogen storage disease type II): clinical features and enzyme replacement therapy. *Acta Neurol Belg* 2006; 106: 82–6.
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8. Fukuda T, *et al.* Acid alpha-glucosidase deficiency (Pompe disease). *Curr Neurol Neurosci Rep* 2007; 7: 71–7.
9. Rossi M, *et al.* Long-term enzyme replacement therapy for Pompe disease with recombinant human alpha-glucosidase derived from Chinese hamster ovary cells. *J Child Neurol* 2007; 22: 565–73.
10. Chen L-R, *et al.* Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease. *J Pediatr* 2009; 155: 271–5.
11. Llerena JC, *et al.* The Brazilian consensus on the management of Pompe disease. *J Pediatr* 2009; 155 (suppl 2): S47–S56.
12. Chien Y-H, *et al.* Pompe disease in infants: improving the prognosis by newborn screening and early treatment. *Pediatrics* 2009; 124: e1116–e1125. Available at: http://pediatrics.aappublications.org/cgi/reprint/124/6/e1116 (accessed 12/02/10)

Adverse Effects, Treatment, and Precautions

Fever, flushing, diarrhoea, vomiting, rash, urticaria, cough, upper respiratory-tract infections, otitis media, pneumonia, tachycardia, tachypnoea, and hypoxia have been commonly reported with alglucosidase alfa. Cardiac arrest has also been reported. Patients with an acute illness at the time of infusion are at greater risk of developing cardiorespiratory failure. Severe cutaneous reactions including ulcerative and necrotising lesions have also been seen with alglucosidase alfa.

Infusion reactions are common with alglucosidase alfa; symptoms may resolve on decreasing the infusion rate, temporarily stopping the infusion, and/or use of antihistamines, corticosteroids, or antipyretics, which may also be given as pre-treatment. Severe reactions may require stopping the infusion immediately. Serious hypersensitivity reactions, including anaphylactic shock, have also been reported during infusion of alglucosidase alfa. Patients with advanced Pompe disease may have compromised cardiac function and should be monitored closely since they may be predisposed to a higher risk of severe complications from infusion reactions.

IgG antibodies to alglucosidase alfa develop in the majority of patients within the first 3 months of treatment, although the effect on long-term efficacy is not clear. The presence of antibodies may predispose patients to developing infusion reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Myozyme; *Belg.*: Myozyme; *Braz.*: Myozyme; *Canad.*: Myozyme; *Cz.*: Myozyme; *Denm.*: Myozyme; *Fr.*: Myozyme; *Ger.*: Myozyme; *Gr.*: Myozyme; *Hong Kong*: Myozyme; *Irl.*: Myozyme; *Israel*: Myozyme; *Ital.*: Myozyme; *Malaysia*: Myozyme; *Neth.*: Myozyme; *Norw.*: Myozyme; *NZ*: Myozyme; *Pol.*: Myozyme; *Port.*: Myozyme; *Spain*: Myozyme; *Swed.*: Myozyme; *Switz.*: Myozyme; *UK*: Myozyme; *USA*: Lumizyme; Myozyme.

Multi-ingredient Preparations. *Canad.*: Digesta.

Acid Fuchsine

Acid Magenta; Acid Roseine; Acid Rubine; CI Acid Violet 19; Colour Index No. 42685; Fucsina ácida; Rubina ácida; Кислый Фуксин.
CAS — 3244-88-0.

Profile

Acid fuchsine is the disodium or diammonium salt of the trisulfonic acid of magenta. It is used as a microscopic stain and a pH indicator.

Acitazanolast *(rINN)*

Acitazanolastum; WP-871; Ацитазаналаст.
3′-(1*H*-tetrazol-5-yl)oxanilic acid.
$C_9H_7N_5O_3$=233.2
CAS — 114607-46-4.
UNII — 99Y8VJ356G (anhydrous acitazanolast); U6SU9ZSU4K (acitazanolast hydrate).

Profile

Acitazanolast is a leukotriene inhibitor used as the hydrate in a concentration of 0.1% in eye drops for the treatment of allergic conjunctivitis (p. 611.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Zepelin.

Aconite

Acetylbenzoylaconine (aconitine); Aconit; Aconit napel; Aconite Root; Aconiti Tuber; Acónito; Aconitum napellus; Amapelo; Anapelo; Matalobos; Monkshood Root; Napelo; Radix Aconiti; Vedegambre azul; Wolfsbane Root; Аконит; Борец; Царь-зелье.
8-Acetoxy-3,11,18-trihydroxy-16-ethyl-1,6,19-trimethoxy-4-methoxymethylaconitan-10-yl benzoate (aconitine).
$C_{34}H_{47}NO_{11}$=645.7 (aconitine)
CAS — 8063-12-5 (aconite); 302-27-2 (aconitine).
ATC Herb — HM02AX5001 (Aconitum napellus: root).
UNII — U0NQ8555JD (Aconitum napellus); KPD2N7348X (Aconitum napellus, root).

NOTE. Wolfsbane is also used as a common name for arnica flower (p. 2447.2).

Description. Aconite consists of the dried tuberous root of *Aconitum napellus* agg. (Ranunculaceae). It contains several alkaloids, the main pharmacologically active one being aconitine.

Pharmacopoeias. *Chin.* and *Jpn* include the root of various *Aconitum* spp.

Uses and Administration

Aconite liniments have been used in the treatment of neuralgia, sciatica, and rheumatism. Sufficient aconitine may be absorbed through the skin to cause poisoning; liniments should never be applied to wounds or abraded surfaces. Aconite should not be used internally because of its low therapeutic index and variable potency; however it is reported to be a common ingredient in traditional Chinese remedies and is also an ingredient of some cough mixtures.

Homoeopathy

Aconite has been used in homoeopathic medicines under the following names: Aconitum, radix; Aconitum, rad.

The whole plant, Aconitum napellus (Aconitum nap), is also used in homoeopathic medicine as is the root of the related plant Aconitum ferox (Aconitum fer).

Adverse Effects and Treatment

Aconite has variable effects on the heart leading to heart failure. It also affects the CNS.

Symptoms of aconite poisoning may appear within minutes or up to 2 hours after oral ingestion; in fatal poisoning death usually occurs within 12 hours, although with larger doses it may be instantaneous.

Initial symptoms (and an important diagnostic feature) are tingling sensations of the tongue, mouth, fingers, and toes followed by generalised paraesthesia. Other symptoms include nausea, vomiting, diarrhoea, muscle weakness, skeletal muscle paralysis, and difficult respiration; also sweats, chills and a feeling of intense cold may occur. Respiratory paralysis, hypotension, and cardiac arrhythmias may develop in severe cases.

Although the benefits of gastric decontamination are uncertain, gastric lavage may be tried in patients within one hour of life-threatening oral poisoning; activated charcoal may also be considered. Patients should be observed and

monitored, and corrective and supportive treatment given as necessary. Arrhythmias are relatively resistant to treatment, although atropine has been tried for bradycardia.

Poisoning. References to poisoning with aconite.

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Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: No-Tos Adultos; *Austria*: Rheuma; *Belg.*: Saintbois; *Braz.*: Expectomel; Melagriao; *Cz.*: Pleumolysin; *Jpn*: Daibofuto; Keishikajutsubuto; Maobushisaishinto; Shimbuto; *Pol.*: Padma 28; *Rus.*: Wantong Artiplas (Вань-тун Артиплас); *Switz.*: Arteria-vita; Padma 28; Padmed Circosan; *UK*: Padma 28.

Homoeopathic Preparations. *Austral.*: Calm; Childrens Cold and Flu Relief; Childrens Cough Relief; Childrens Sleep; Pain & Fever Relief; Respatona Dry Cough & Nasal Congestion; Respatona Head Cold; Sedatif†; Teething Relief; *Austria*: Aconitum Med Complex; Aflubin; Apozema Allium Cepa compositum; Ferrum Phosphoricum comp; Gripp Heel; Infludo; Lobelia Med Complex; Luffa Med Complex; Meditonsin; Metavirulent; Nisylen†; Otovowen; Pneumodoron Nr 1; toxi-loges; Traumeel; *Canad.*: Aches & Pains; Arum Triphyllum Plex†; Barijodeel†; Bryaconeel†; Calms Forte 4 Kids; Calnor†; Calsom†; Cold Tablets with Zinc†; Comp-Drops 3 Bowel Support†; Cough Syrup with Honey†; Crou Complex†; Echinacea Compositum; Formula INF; Homeovox; Hylands Formula CS; Hylands Formula CZ; Hylands LCQ; Hylands Leg Cramps; Ivermax; L52 Cough & Cold; Leg Cramps with Quinine; Sedatil; Spascupreel; Traumeel; *Chile*: Bioactiv Z; *Cz.*: Gripp Heel; Homeovox; Lehnigrip†; Sedatif PC; Spascupreel S†; Traumeel; *Fr.*: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 18†; Abbe Chaupitre no 1†; Abbe Chaupitre no 20†; Abbe Chaupitre no 25†; Abbe Chaupitre no 66†; Abbe Chaupitre no 6; Abbe Chaupitre no 91†; Aconium Compose†; Arnica Complexe no 1; Arum Triphyllum Compose; Baudry; Boripharm No 11†; Boripharm No 1†; Crataegus Complexe No 15; Euphrasia Complexe No 115; Gelsemium Complexe No 70; Geranium Complexe No 108†; Homeogrippe†; Homeovox; Infludo; Iodum Complexe No 118; L 52; Pates Pectorales; Pulsatilla Complexe No 60†; Ranunculus Complexe No 79; Rheumadoron; Rhododendron Complexe No 42†; Rhus Toxicodendron Complexe No 80; Sclero-Drainol†; Sedatif PC; Urtica Complexe No 82†; Uva Ursi Complexe No 9; *Ger.*: Aconitum Nicotiana comp†; Anovin; Arnica comp/Apis†; Arnica Oligoplex; Arnica/Symphytum comp; Asthmavowen-N†; Aurum-Gastreu S R2; Cefagrippin†; Contramutan; Echinacin akut; Erkaltungs-Entoxin; Eupatorium N Oligoplex; Febrocyl L Ho-Len-Complex; Ferrum phosphoricum comp; Gelsemium Comp; Gelsemium Comp; Gelsemium N Oligoplex; Gnaphalium Injektopas SL; Gripp-Heel; Grippe-Gastreu S R6; Gripps; HanoToxin M; Hanotoxin M; Infekt 1-Injektopas N; Infekt-Komplex L Ho-Pu-Complex; Infi-Echinacea; Infigripp; Infihepan; Infludo; Influex; Influvit; Jowidarmin; Jsoskleran; Mato; Meditonsin; metavirulent; Migrane Hevert†; Migrane Hevert; Natuimmun†; Neuralgie-Gastreu R70; Nisylen; Original-Tinktur N Truw; Otofren; Otovowen; Pascoleucyn; phono Gripp; Pneumodoron 1; Rheumodoron 102 A; Rheumodoron 1; Rufebran neuro†; Schworotox A; Spascupreel; Tonsillosyx; toxi-loges; toxi-loges; Traumeel S; Tussistin; Viscum album H†; Wiedimmun N†; Wiedimmun; *Hung.*: Aflubin; Gripp-Heel; Homeovox; Sedatif; Spascupreel; Traumeel; *Neth.*: Arnillte; Cold Care; Echilite; Febrilite; Gripp-Heel H; Grippe-Gastreu R6; Head Care; Homeocare Revito; Homeovox; Infludo; Kind 0-6 Kindtherm; Kind 0-6 Nisykind; Kruidvat Homeopathie Influcomplex†; Nervival; Nisyleen; Sedatif PC; Traumeel S; *Port.*: Homeovox; Sedatif PC; *Rus.*: Aflubin (Афлубин); Belladonna-Plus (Белладонна-Плюс); Briacon (Бриакон); Homeostres (Гомеострес); Homeovox (Гомеовокс); Influcid (Инфлюцид); Traumeel S (Траумель С); *S.Afr.*: Ferrum Phos Comp†; Gripp-Heel; Infludo†; Pneumodoron 1†; Rheumadoron†; Traumeel S; *Switz.*: Gripp-Heel; Homeovox; Influaforce†; Infludo; metavirulent; Regenaplex Nr 41a; Regenaplex Nr. 21c; Regenaplex Nr. 31c; Rheumadoron; Sedatif PC; Traumeel; *UK*: Infludo; Rheumadoron; Rheumadoron; *Ukr.*: Aflubin (Афлубин); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Homeovox (Гомеовокс); Influcid (Инфлюцид); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); *USA*: Preferred Remedies Cold & Flu; Traumeel; *Venez.*: Traumeel.

Acridine Orange

Naranja de acridina; Акридиновый Оранжевый.
3,6-Bis(dimethylamino)acridine.
$C_{17}H_{19}N_3$=265.4
CAS — 494-38-2.
UNII — F30N4O6XW.

Profile

Acridine orange is a dye with antiseptic properties. It has been used as a diagnostic stain in microbiology.

For details of the antiseptic properties of acridine derivatives, see p. 1732.3.

Diagnostic use. Acridine orange has been used for the diagnostic staining of malarial parasites in the quantitative buffy coat (QBC) technique.[1-6] Acridine orange stains the DNA of the malarial parasites in a blood sample that is then centrifuged, and the area just below the buffy coat is examined under a fluorescence microscope. It has been described as easier and quicker to use than the standard examination of stained blood films, and is therefore seen to be advantageous when urgent diagnosis is needed, and in endemic areas where a high number of tests need to be performed in a short period of time and/or technical staff are inexperienced. However, malarial species identification is not always possible and sensitivity may be poor particularly at low levels of parasitaemia. Additionally, the initial outlay for special equipment such as a micro-centrifuge and a fluorescence or adapted light microscope and ongoing expense of the QBC kits may be prohibitive in developing countries.

The QBC technique has also been used in the diagnosis of other diseases such as babesiosis, filariasis, and trypanosomiasis.

Acridine orange has also been tried for the staining of blood slides.[7-10]

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Acrolein

Acraldehyde; Acrialdehído; Acroleína; Acrylaldehyde; Acrylic Aldehyde; Allialdehído; Propenal.
Prop-2-enal.
C_3H_4O=56.06
CAS — 107-02-8.
UNII — 7864XYD3JJ.

Profile

Acrolein is a volatile, highly flammable liquid at ordinary temperature and pressure. It has various industrial uses, but is also a toxic byproduct of combustion and may be present in exhaust gases, tobacco smoke, and smoke from fires. It is irritant to the skin and may cause skin burns. Ingestion of acrolein produces severe gastrointestinal distress. The vapour causes lachrymation and pulmonary irritation. Inhalation may cause pulmonary oedema and permanent lung damage.

Acrolein is a metabolite of cyclophosphamide (p. 771.1) and may be responsible for the latter's bladder toxicity.

References.
1. WHO. Acrolein. *IPCS Health and Safety Guide 67*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg067.htm (accessed 23/07/08)
2. WHO. Acrolein. *Environmental Health Criteria 127*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc127.htm (accessed 23/07/08)
3. Stevens JF, Maier CS. Acrolein: sources, metabolism, and biomolecular interactions relevant to human health and disease. *Mol Nutr Food Res* 2008; 52: 7–25.
4. Faroon O, *et al.* Acrolein health effects. *Toxicol Ind Health* 2008; 24: 447–90.

Acrylamide

Acrilamida; Akryloamid; Amida acrilica; Etilencarboxamida; Vinil amida.
Propenamide.
C_3H_5NO=71.08
CAS — 79-06-1.
UNII — 20R035KLCI.

Profile

Acrylamide is highly toxic and irritant; it can be absorbed through unbroken skin. Symptoms of poisoning include burning and ulceration of the mouth and throat following ingestion. Excessive sweating is common and other symptoms may include numbness of limbs, paraesthesias, and muscle weakness. CNS effects such as somnolence, confusion, hallucinations, ataxia, tremors, dysarthria, and nystagmus may occur depending on the severity of exposure. Peripheral neuropathies may appear several weeks after severe acute exposure or as a result of chronic exposure. Gastric lavage may be tried in patients within one hour of ingestion, although some recommend gastric aspiration instead of lavage; activated charcoal may also be considered, but ipecacuanha-induced emesis is not recommended because of the risk of CNS depression and seizures. Contamination of eyes and skin should be irrigated and treated as for burns. Patients should be monitored, and corrective and supportive treatment given as necessary.

Acrylamide has various industrial applications, including use as a plasticiser and a waterproof 'chemical grout'.

References.
1. Kesson CM, *et al.* Acrylamide poisoning. *Postgrad Med J* 1977; 53: 16–17.
2. WHO. Acrylamide. *IPCS Health and Safety Guide 45*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg045.htm (accessed 31/03/06)
3. Exon JH. A review of the toxicology of acrylamide. *J Toxicol Environ Health B* 2006; 9: 397–412.

Food toxicity. Concerns have been expressed by the Swedish National Food Administration about the level of acrylamide they found in certain cooked foods, particularly those exposed to very high temperatures such as fried foods, and the potential carcinogenic risk. However, it was acknowledged that, although the results have been replicated in other international laboratories, the total sample size was small and none of the methods being used have so far been validated.[1] One subsequent population-based study failed to find any excess risk or convincing trend of cancer of the bowel, bladder, or kidney in high consumers of foods with a high or moderate acrylamide content.[2] The joint FAO/WHO Expert Committee on Food Additives (JECFA)[3] reviewed data provided by 24 countries on acrylamide in food analysed between 2002 and 2004. Their recommendations were for re-evaluation of the effects of acrylamide on completion of studies of carcinogenicity and neurotoxicity, and that efforts to reduce the concentrations of acrylamide in food should continue.

1. Kapp C. WHO urges more research into acrylamide in food. *Lancet* 2002; 360: 64.
2. Mucci LA, *et al.* Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. *Br J Cancer* 2003 88: 84–9.
3. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the Joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 18/07/08)

Actinoquinol Sodium *(USAN, rINNM)*

Actinoquinol sódico; Actinoquinol Sodique; Natrii Actinoquinolum; Sodium Etoquinol; Sodium Tequinol; Натрий Актиноквинол.
Sodium 8-ethoxy-5-quinolinesulfonate.
$C_{11}H_{10}NNaO_4S$=275.3
CAS — 15301-40-3 (actinoquinol); 7246-07-3 (actinoquinol sodium).
UNII — 8PW272ITDS.

Profile

Actinoquinol and actinoquinol sodium have been used as ingredients in eye drop preparations intended to protect the eyes from the effects of light.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Uvicol†; *Ger.*: duraultra†; *Ital.*: Fotofil.

Ademetionine *(rINN)*

Ademethionine; Ademetioniini; Ademetionin; Ademétionin; Ademetionina; Ademetioninum; *S*-Adenosyl-L-methionine; Methioninyl adenylate; SAMe; Адеметионин.
(*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulphonio]-5′-deoxyadenosine hydroxide, inner salt.
$C_{15}H_{22}N_6O_5S$=398.4

CAS — 29908-03-0; 485-80-3; 17176-17-9.
ATC — A16AA02.
ATC Vet — QA16AA02.
UNII — 7LP2MPO46S.

Ademetionine Sulfate Tosilate

Ademetionine Disulfate Tosylate; S-Adenosyl-L-methionine Sulfate Tosilate; FO-1561.
CAS — 55722-12-8.
UNII — 564ROC9U09.

Pharmacopoeias. In *US*.

USP 36: (*S*-Adenosyl-L-methionine Disulfate Tosylate). A white powder. Freely soluble in water. Store in airtight containers in a refrigerator at a temperature between 2 degrees and 8 degrees. Protect from light.

Profile

Ademetionine is a naturally occurring molecule found in virtually all body tissues and fluids. It acts as a methyl group donor in many transmethylation reactions and therefore is involved in the synthesis or metabolism of several compounds that maintain normal cell function. Ademetionine sulfate tosilate and ademetionine butanedisulfonate are stable forms of ademetionine that have been promoted for the treatment of depression (see below), liver disorders, and musculoskeletal and joint disorders such as osteoarthritis and fibromyalgia (see below).

References.

1. Bottiglieri T, *et al.* The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. *Drugs* 1994; 48: 137–52.
2. Chavez M. SAMe: S-adenosylmethionine. *Am J Health-Syst Pharm* 2000; 57: 119–23.
3. Ferrow CW, Avila JR. Efficacy of the dietary supplement S-adenosyl-L-methionine. *Ann Pharmacother* 2001; 35: 1414–25.
4. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): from the bench to the bedside—molecular basis of a pleiotrophic molecule. *Am J Clin Nutr* 2002; 76 (suppl): 1151S–1157S.
5. Gören JL, *et al.* Bioavailability and lack of toxicity of S-adenosyl-L-methionine (SAMe) in humans. *Pharmacotherapy* 2004; 24: 1501–7.

Depression. Ademetionine has been given orally or parenterally in the management of depression (p. 398.1). It appears to be of similar efficacy to the tricyclic antidepressants but evidence is limited to small, heterogeneous groups of patients studied over short periods of time; additionally many studies have involved parenteral rather than oral therapy.

References.

1. Bressa GM. S-Adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994; 154 (suppl): 7–14.
2. Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr* 2002; 76: 1158S–1161S.
3. Papakostas GI, *et al.* S-Adenosyl-methionine in depression: a comprehensive review of the literature. *Curr Psychiatry Rep* 2003; 5: 460–6.
4. Williams AL, *et al.* S-adenosylmethionine (SAMe) as treatment for depression: a systematic review. *Clin Invest Med* 2005; 28: 132–9.

Liver disorders. Some workers have found that ademetionine produced clinical improvement in patients with **intrahepatic cholestasis,**[1,2] including that associated with pregnancy.[3,4] Pruritus associated with the condition has also been relieved. Other studies,[5,6] however, have not found any benefit.

Ademetionine produced a good or excellent clinical response in patients with **hepatic steatosis.**[7] In a study[8] of patients with **alcoholic liver cirrhosis,** treated with ademetionine for 2 years, there was a trend towards reduced overall mortality or need for liver transplantation, but only in patients with less severe hepatic dysfunction. However, a systematic review[9] of 9 randomised placebo-controlled studies, which included the latter study could not find evidence to support or refute the claim that ademetionine has a beneficial effect in patients with alcoholic liver diseases, and larger high quality randomised placebo-controlled studies are needed.

1. Frezza M, *et al.* Oral S-adenosylmethionine in the symptomatic treatment of intrahepatic cholestasis: a double-blind, placebo-controlled study. *Gastroenterology* 1990; 99: 211–15.
2. Almasio P, *et al.* Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. *Drugs* 1990; 40 (suppl 3): 111–23.
3. Bonfirraro G, *et al.* S-Adenosyl-L-methionine (SAMe)-induced amelioration of intrahepatic cholestasis of pregnancy: results of an open study. *Drug Invest* 1990; 2: 125–8.
4. Frezza M, *et al.* S-Adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy: results of a controlled clinical trial. *Hepatogastroenterology* 1990; 37 (suppl 2): 122–5.
5. Ribalta J, *et al.* S-Adenosyl-L-methionine in the treatment of patients with intrahepatic cholestasis of pregnancy: a randomized, double-blind, placebo-controlled study with negative results. *Hepatology* 1991; 13: 1084–9.
6. Floreani A, *et al.* S-Adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol* 1996; 67: 109–13.
7. Caballeria E, Moreno J. Therapeutic effects of S-adenosylmethionine (SAMe) in hepatic steatosis. *Acta Ther* 1990; 16: 253–64.
8. Mato JM, *et al.* S-Adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 1999; 30: 1081–9.
9. Rambaldi A, Gluud C. S-Adenosyl-L-methionine for alcoholic liver diseases. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/04/08).

Musculoskeletal and joint disorders. Ademetionine has been reported[1-5] to possess therapeutic efficacy in the treatment of osteoarthritis (p. 12.3) and similar conditions, possibly due to an effect on cartilage metabolism and formation of anti-inflammatory mediators within the cell; it may also inhibit leukotrienes but does not appear markedly to interfere with prostaglandin synthesis. However, a systematic review[4] found that available studies were mainly small and of questionable quality, and therefore the routine use of ademetionine for osteoarthritis of the knee or hip could not be recommended until further evaluation through larger randomised controlled studies. Possible benefit in fibromyalgia (see under Soft-tissue Rheumatism, p. 14.2) has also been shown.[5]

1. Domljan Z, *et al.* A double-blind trial of ademethionine vs naproxen in activated gonarthrosis. *Int J Clin Pharmacol Ther Toxicol* 1989; 27: 329–33.
2. Bradley JD, *et al.* A randomized, double blind, placebo controlled trial of intravenous loading with S-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J Rheumatol* 1994; 21: 905–11.
3. Soeken KL, *et al.* Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. *J Fam Pract* 2002; 51: 425–30.
4. Najm WI, *et al.* S-Adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. *BMC Musculoskelet Disord* 2004; 5: 6.
5. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_1101201015433 1.pdf (accessed 16/08/10)
6. Rutjes AW, *et al.* S-Adenosylmethionine for osteoarthritis of the knee or hip. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/07/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tunik; ***China***: Transmetil (思美泰); ***Cz.***: Transmetil; ***Ger.***: Gumbaral†; ***India***: Ostisave; ***Ital.***: Donamet; Samyr; Transmetil; ***Mex.***: Samyr; ***Rus.***: Heptor (Гептор); Heptral (Гептрал); ***Singapore***: Heptral; ***Ukr.***: Heptral (Гептрал).

Multi-ingredient Preparations. ***Arg.***: Tunik B12; ***Ital.***: Selene.

Adenine

Adeniini; Adenin; Adenina; Adeninas; Adénine; Adeninum; Vitamin B_4; Vitamina B_4; Аденин.
6-Aminopurine; 1,6-Dihydro-6-iminopurine.
$C_5H_5N_5$=135.1
CAS — 73-24-5.
UNII — JAC85A2161.

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

Ph. Eur. 8: (Adenine). A white or almost white powder. Very slightly soluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

USP 36: (Adenine). Odourless white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in boiling water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Profile

Adenine is a purine base and one of the components of adenosine nucleotides that form nucleic acids (p. 2573.1). It is also a constituent of many coenzymes. It has been used to extend the storage life of whole blood (p. 1135.2) and has also been given for the management of white blood cell disorders and alcoholism. Adenine hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Leuco-4†.

Multi-ingredient Preparations. ***Philipp.***: Godex; Inlex; Mitocore; Mitonerb; Mivex; ***Rus.***: Lidevine (Лидевин); ***Spain***: Pleon†; ***Ukr.***: Hepadif (Гепадиф); Lidevin (Лидевин).

Pharmacopoeial Preparations
USP 36: Anticoagulant Citrate Phosphate Dextrose Adenine Solution.

Adenosine Phosphate *(BAN, USAN, rINN)*

A-5MP; Adenosina, fosfato de; Adenosine 5′-Monophosphate; Adenosine Monophosphate; Adénosine, Phosphate d'; Adenosine-5′-(dihydrogen phosphate); Adenosine-5′-phosphoric Acid; Adenosini Phosphas; AMP; Fosfato de adenosina; Monophosadénine; Muscle Adenylic Acid; NSC-20264; Аденозина Фосфат; 5′-Adenylic Acid.
6-Amino-9-β-D-ribofuranosylpurine 5′-(dihydrogen phosphate).
$C_{10}H_{14}N_5O_7P$=347.2
CAS — 61-19-8.
ATC — C01EB10.
ATC Vet — QC01EB10.
UNII — 415SHH325A.

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{12}N_5Na_2O_7P.xH_2O$).

Profile

Adenosine phosphate is an endogenous adenine nucleotide involved in many biological processes. Adenosine monophosphate (AMP) is a vasodilator and has been included in preparations for venous insufficiency, haemorrhoids, and varicose veins. It has also been used in pain and inflammation. Adenosine diphosphate and its disodium salt have also been used. AMP is also used in bronchial challenge tests to assess airway hyper-responsiveness in asthma and other respiratory disorders.

Unlike adenosine (p. 1291.1) or adenosine triphosphate (below), adenosine phosphate is not used in supraventricular tachycardias.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ming Sheng (铭生); Tian An Xin (天安欣); Wei An (苇安); Wo Ping (沃平); Xiao Shan Ping (肖山平); ***Fr.***: Adenyl; ***Rus.***: Phosphaden (Фосфаден).

Multi-ingredient Preparations. ***Fr.***: Surelen†; ***Gr.***: Arkadin; ***Indon.***: Nevradin†; ***Spain***: Artri†; Pleo Vitamin†.

Adenosine Triphosphate

Ácido adeniltrifosfórico; Ácido adenosintrifosfórico; Adenosina, trifosfato de; Adenosine 5′-Triphosphate; Adenylpyrophosphoric Acid; ATP; Trifosadenina; Triphosadénine; Аденозинтрифосфат; 5′-Adenyldiphosphoric Acid.
Adenosine 5′-(tetrahydrogen triphosphate).
$C_{10}H_{16}N_5O_{13}P_3$=507.2
CAS — 56-65-5.
ATC — C01EB10.
ATC Vet — QC01EB10.
UNII — 8L70Q75FXE.

Pharmacopoeias. *Ger.* includes the disodium salt ($C_{10}H_{14}N_5Na_2O_{13}P_3$=551.1).

Profile

Adenosine triphosphate (ATP) is an endogenous adenine nucleotide with a fundamental role in cellular energy transformation; ATP is hydrolysed to adenosine diphosphate (ADP) releasing energy stored in phosphate bonds. In addition, extracellular ATP influences many biological processes.

ATP is a vasodilator that has been used in varied disorders. The sodium and disodium salts have been used in cerebral and peripheral vascular disorders and also for the treatment of supraventricular tachycardias, although adenosine (p. 1291.1) is the form generally used as an antiarrhythmic. ATP has also been investigated for use in cachexia in patients with cancer.

Reviews.

1. Agteresch HJ, *et al.* Adenosine triphosphate: established and potential clinical applications. *Drugs* 1999; 58: 211–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xin Long Ning (新隆宁); ***Fr.***: Atepadene†; Striadyne; ***Hong Kong***: ATP Daiichi; ***Jpn***: Adetphos; ***Philipp.***: Adepos; Nutaphake; ***Rus.***: Fosfobion (Фосфобион); ***Spain***: Atepodin.

Multi-ingredient Preparations. ***Arg.***: Fospartan Ginseng; ***Canad.***: Vitathion-ATP†; ***China***: Ai Nuo Ji (艾诺吉); Jia You (佳优); ***Indon.***: Bio-ATP; Enerplus; Myoviton; Nichoviton; Pro ATP; Vitap; ***Jpn***: Panion; ***Spain***: Refulgin†; Tomevit†; ***Ukr.***: Cocarnit (Кокарнит).

Adiphenine *(rINN)*

Adifenina; Adiphénine; Adipheninum; Адифенин.
2-Diethylaminoethyl diphenylacetate.
$C_{20}H_{25}NO_2$=311.4
CAS — 64-95-9.
UNII — YKG6OR043Q.

Adiphenine Hydrochloride (USAN, rINN)

Adifenina; Adifenina, hidrocloruro de; Adiphenine, Chlorhydrate d'; Adiphenini Hydrochloridum; Cloridrato de Adifenina; Hidrocloruro de adifenina; NSC-129224; Spasmolytine; Адифенина гидрохлорид.

$C_{20}H_{25}NO_2.HCl$=347.9

CAS — 50-42-0.

UNII — 4284PDY0AV.

Profile

Adiphenine and adiphenine hydrochloride have been used as antispasmodics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Doriless; Doriless; Lisador; Lisantil; Sedador; Sedalene; Sedalin†; *Chile*: Abalgin; Abalgin; SAE; *Turk.*: Spasmo-Panalgine.

Adipic Acid

Acide adipique; Ácido hexanodioico; Acidum adipicum; Adipico, ácido; Adipiinihappo; Adipinsäure; Adipinsav; Adipinsyra; Adipo rūgštis; Hexanedioic Acid; Kwas adypinowy; Kyselina adipová; Адипиновая Кислота.

1,4-Butanedicarboxylic acid.

$C_6H_{10}O_4$=146.1.

CAS — 124-04-9.

UNII — 76A0JE0FKJ.

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

Ph. Eur. 8: (Adipic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water; freely soluble in alcohol and in methyl alcohol; soluble in acetone.

USNF 31: (Adipic Acid). A white, crystalline powder. Slightly soluble in water; soluble in boiling water and in acetone; freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

Profile

Adipic acid is used as an acidifier in pharmaceutical products and in foods and has been included in preparations for the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Bouillet.

Adonis Vernalis

Adonide; Adonidis Vernalis Herba; Adonis; Adonis de primavera; Adonis vernal; Adoniskraut; False Hellebore; Herba Adonidis; Vernal Pheasant's Eye; Ziele miłka wiosennego; Горицвет Весенний.

ATC Herb — HC01AX5001 (Adonis vernalis herb).

UNII — DX3ZNI25WK.

Pharmacopoeias. In *Ger.* and *Pol.*

Profile

Adonis vernalis, the dried aerial parts of *Adonis vernalis* (Ranunculaceae), contains cardiac glycosides which have actions similar to those of digoxin (p. 1353.3).

Homoeopathy

Adonis vernalis has been used in homoeopathic medicines under the following names: Adonis; Adonis v.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Rimoneuran; Serenus; *Ger.*: Miroton†; *Mex.*: Verisan Triplex; *Rus.*: Cardiovalen (Кардиовален).

Homoeopathic Preparations. *Austria*: Homviocorin; *Fr.*: Vespa Complexe No 46†; *Ger.*: Angioton H; Angioton S†; Convallocor; Convallysan M; Lowe-Komplex Nr 10; Truw Gold; *Ukr.*: Homviocorin-N (Хомвіокорин-N).

Adrenalone (USAN, pINN) ⊗

Adrenalon; Adrenalona; Adrénalone; Adrenaloni; Adrenalonum; Адреналон.

3′,4′-Dihydroxy-2-(methylamino)acetophenone.

$C_9H_{11}NO_3$=181.2.

CAS — 99-45-6.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

UNII — EGU41QL329.

Adrenalone Hydrochloride (pINN) ⊗

Adrenalona, hidrocloruro de; Adrénalone, Chlorhydrate d'; Adrenaloni Hydrochloridum; Adrenalonu chlorowodorek; Hidrocloruro de adrenalona; Адреналона гидрохлорид.

$C_9H_{11}NO_3.HCl$=217.6

CAS — 62-13-5.

ATC — A01AD06; B02BC05.

ATC Vet — QA01AD06; QB02BC05.

UNII — NN82YWE2IC.

Profile

Adrenalone hydrochloride is used as a local haemostatic and vasoconstrictor. It has also been used with adrenaline in eye drops for glaucoma.

Aesculus

Aesculus hippocastanum; Castaño de indias; Falso castaño; Hippocastani semen; Horse-chestnut; Marron d'Inde; Rosskastaniensamen; Spanish Chestnut; Конский Каштан.

CAS — 6805-41-0 (aescin); 11072-93-8 (β-aescin); 531-75-9 (anhydrous esculoside).

ATC Herb — HA07XA5001 (Aesculus hippocastanum bark); HD03WX5001 (Aesculus hippocastanum bark); HR05DB5001 (Aesculus hippocastanum leaf); HC05CW5001 (Aesculus hippocastanum leaf); HC05CW5002 (Aesculus hippocastanum seed); HC05BW5001 (Aesculus hippocastanum seed).

UNII — 2331W47PSX (Aesculus hippocastanum); 7U76MXL14N (Aesculus hippocastanum bark); KK0Z92IIBM (Aesculus hippocastanum flower); Z49U891FNO (Aesculus hippocastanum leaf); 3C18L6RUAZ (Aesculus hippocastanum seed).

NOTE. The name Spanish Chestnut has been applied both to Aesculus and to Sweet Chestnut (p. 2625.1).

Pharmacopoeias. In *Pr.*, *Ger.*, *It.*, and *US*.

US also includes the powdered form and powdered extract.

Ger. also includes esculoside in the sesquihydrate form.

USP 36: (Horse Chestnut). The dried seeds of *Aesculus hippocastanum* (Hippocastanaceae), harvested in the autumn. It contains not less than 3.0% of triterpene glycosides, calculated on the dried basis as aescin. Protect from light and moisture.

Uses and Administration

The seeds (conkers) and other parts of the horse-chestnut, *Aesculus hippocastanum*, contain several active principles including esculoside (aesculin or esculin; 6-β-D-glucopyranosyloxy-7-hydroxycoumarin, $C_{15}H_{16}O_9$=340.3) and aescin (escin), which is a mixture of saponins.

Aescin and esculoside, the major active principles of aesculus, have been used in the prevention and treatment of various peripheral vascular disorders, including haemorrhoids (p. 1808.1). They have been given orally, by intravenous injection (in the form of sodium aescinate), by rectal suppository, and applied topically. Aescin has also been given intravenously in the prevention and treatment of postoperative oedema.

Other derivatives such as sodium aescin polysulfate have also been used.

Homoeopathy

Aesculus has been used in homoeopathic medicines under the following names: Aesculus hippocastanum; Aesculus hipp; Aesculus cortex; Aesculus hippocastanum ex cortice; Aesc. hip.; Aesculus hippocastanum, flos; Aesculus hipp, flos.

Related plants are also used in homoeopathic medicines under the following names: Aesculus carnea, flos; Aesculus glabra; Aesculus glab.

Esculoside has been used in homoeopathic medicines under the following names: Aesculinum; Aescul.

General references.

1. WHO. Semen Hippocastani. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/15.html (accessed 04/02/10)

The use of aesculus has been reviewed,[1-3] although there is some evidence suggesting benefit in chronic venous insufficiency, more rigorous studies are needed.[2]

1. Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. *Pharmacol Res* 2001; 44: 183–93.
2. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2006 (accessed 31/03/06).
3. Anonymous. Aesculus hippocastanum (Horse chestnut). *Altern Med Rev* 2009; 14: 278–83.

Adverse Effects

Ingestion of aesculus may cause nausea, vomiting, diarrhoea, abdominal colic, delirium, and with large doses respiratory arrest (but see under Poisoning, below).

Effects on the kidneys. A report of the incidence of acute renal failure in patients after cardiac surgery and implicating high-dose intravenous aescin therapy.[1] In 70 patients given a mean maximum daily dose of 340 micrograms/kg, no alteration of renal function was seen; in 16 receiving 360 micrograms/kg, mild renal impairment occurred; and in 40 given 510 micrograms/kg, acute renal failure developed.

1. Helberg K, *et al.* Medikamentöse bedingtes post-operatives Nierenversagen nach herzchirurgischen Eingriffen. *Thoraxchirurgie* 1975; 23: 396–400.

Effects on the respiratory tract. Bronchial asthma associated with aescin inhalation has been reported in a worker in the pharmaceutical industry.[1]

1. Muñoz X, *et al.* Occupational asthma related to aescin inhalation. *Ann Allergy Asthma Immunol* 2006; 96: 494–6.

Effects on the skin. Contact dermatitis[1] to esculoside and contact urticaria[2] to aescin have been reported after the use of topical preparations that contained these extracts. Both reactions were confirmed by positive skin tests.

1. Comaish JS, Kersey PJ. Contact dermatitis to extract of horse chestnut (esculin). *Contact Dermatitis* 1980; 6: 150–1.
2. Escribano MM, *et al.* Contact urticaria due to aescin. *Contact Dermatitis* 1997; 37: 233.

Poisoning. There have been reports of poisoning in children from eating the seeds, or drinking infusions made from the leaves and twigs of horse-chestnut trees.[1] The toxic substance is considered to be esculoside. Symptoms of poisoning were muscle twitching, weakness, lack of coordination, dilated pupils, vomiting, diarrhoea, paralysis, and stupor.

The UK National Poisons Information Service considers, however, that given the bitterness of the seeds and the poor gastrointestinal absorption of esculoside, significant poisoning is unlikely.

1. Nagy M. Human poisoning from horse chestnuts. *JAMA* 1973; 224: 213.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Grafic Retard; Herbaccion Venotonico; Nadem; Venastat; Venostasin; *Austria*: Aesculaforce; Provenen†; Reparil; Venosin; Venostasin; *Belg.*: Reparil; Traumatil; Veinofytol; Venoplant; *Braz.*: Phytovein; Reparil; Reparil; Varilise; Venafort; Venotac; Zarv; *Chile*: Venastat; *China*: Ou Kai (欧开); *Cz.*: Reparil; Venitan; Yellon†; *Fin.*: Venaforce†; *Fr.*: Flogencyl; *Ger.*: Aescorin Forte; Aescusan; Aescuven; Essaven Neu†; Essaven†; Heweven Phyto†; Hoevenol; Noricaven; Plissamur; Reparil; Venalot; Venen-Tabletten; Venen-Tropfen N†; Venentabs; veno-biomo†; Venoplant; Venopyronum†; Venorutin retard Rosskastanie†; Venostasin; Venostasin; *Hong Kong*: Reparil; *Hung.*: Venastat; *Irl.*: Venaforce; *Ital.*: Edeven†; Edevexin; Flebostasin; Ginoven; Reparilexin; *Mex.*: Alevarin; Venastat; *Norw.*: Venastat; *Pol.*: Aescuven; Esceven; Hiposem; Reparil; Sapoven; Venastat; Venitan; Venoplant; Venotonin; *Port.*: Varison; *Rus.*: Escizane (Эсцизан); Rectakiv (Ректакив); Venitan (Венитан); Venoplant (Веноплант); *Spain*: Flebostasin; Thrombescina; Varidd†; *Swed.*: Venastat; *Switz.*: Aesculaforce; AesculaMed; Bio-Venaphyt†; Phlebostasin; Venavit N; Venostasin; *Thal.*: Reparil; Reparil; *Turk.*: Reparil; Venotrex; *UK*: Venaforce; *Ukr.*: Aescusan (Эскузан); Aesplant (Эсплант); Eskuvit (Эскувит); Venitan (Венитан); Venoplant (Веноплант); *Venez.*: Vasoplant.

Multi-ingredient Preparations. *Arg.*: CVP Cellulite; Escina Forte; Escina Omega; Esculeol P; Flaval; Grafic Forte; Troxeven; Tubarine; Venofuf; Venostasin; Venostasin; VNS 45; *Austral.*: Aesculus & Ruscus Compound; Extralife Leg-Care†; Horse-chestnut Complex; Sleep Remedy; Vein Relief; Zellulean with Escin†; *Austria*: Amphodyn†; Augentropfen Stulln†; Heparin Comp; Opino; Opino; Reparil; Urelium Neu; *Belg.*: Rectovasol; Reparil; *Braz.*: Hematom; Novarrutina; Proctosan; Reparil; Reparil; Venocur Triplex; *Canad.*: Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; *Chile*: Pectokast; Proctoplex; Reparivex; *China*: Ou Lai (欧莱); Reparil-Gel N (利百雷凝胶); Stulln (施图伦); Stulln (施图伦); *Cz.*: Anavenol; Ophthalmo-Evercil; Reparil-Gel N; *Denm.*: Proctosedyl; *Fin.*: Proctosedyl; *Fr.*: Aphloine P; Arterase; Climaxol; Escinogel†; Evarose†; Histo-Pluine P; Intrait de Marron d'Inde P; Opo-Veinogene; Pelvimag; Phlebocreme; Phlebogel†; Phlebosedol†; Phlebosup; Phytomelis; Rap Phyto; Rap Phyto; Reparil; Sedorrhoide; Veinophytum†; Veinostase; Veinotonyl; Vivene†; *Ger.*: Aescusan†; Augentropfen Stulln Mono; Cefasabal†; Diu Venostasin; Fagorutin Rosskastanien-Balsam N†; Hoevenol; Intradermi†; PC 30 V; Ratanhia comp†; Reparil-Gel N; Schmupfencreme; Sportupac M†; Trauma-cyl†; Varicylum-S†; Weleda Hamorrhoidalzäpfchen; *Gr.*: Opino; *Hong Kong*: Reparil; *Hung.*: Aranyer Illeni; Reparil N; Venen; *India*: Proctosedyl; *Indon.*: Lanaven Plus†; Lanaven; Opino†; *Irl.*: Proctosedyl; *Ital.*: Algorex; Altadrine; Angiovein; Binfollpase; Binfonorm†; Blogofort†; Capill Venogel; Capill; Centella Complex; Centella Complex; Centeril H;

Centeril H; Clebolider†; Criotonal; Dermocinetic; Edeven; Enatus; Essaven; Flavion; Flavion; Flebo-Sl†; Flebolider; Flebovis materna; Flebozin; Flodolor; Flogofort Cremagel; Flogofort; Flogovis IdroGel; Flogovis; Geflon; Inflamase IdroGel; Inflamase; Levital Plus; Lik-Gel†; Linfonorm Cremagel; Liotontrauma; Muscoril Trauma; Osmogel; Osteolip Crema; Pik Gel; Plogovis†; Proctopure; Proctosedyl; Proctosedyl; Recto-Reparil; Reparil CM; Sidenol; Signum; Snell Cell†; Somatoline; Vasotonal; Venactive; Venalta; Venoplant; Venoplant; Venoton; Wasotonal†; *Malaysia*: Cefasabal; Proctosedyl; Reparil-Gel N; *Mex.*: Almodin; Varicyl; Verisan Triplex; *Mon.*: Fluon+; Fluon; Phytospray; *Norw.*: Proctosedyl; *Philipp.*: Proctosedyl; Reparil N; *Pol.*: Aesculan; Anavenol†; Arcalen; Arnisol; Emorect; Escalar; Fitoven; Hemorol; Neo-Aesculan; Proctosone†; Proktosedon; Reparil N; Sapoven AT†; Sapoven T; Savarix; Venacorn; Venescin; Venoforton; Venozel; *Port.*: Synchrocell; Venoparil; *Rus.*: Aescusan (Эскузан); Anavenol (Анавенол); Evalar (Эвалар); Herbion Aesculus (Гербион Эскулюс); Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); Reparil-Gel N (Репарил-Гель Н); Venitan Forte (Венитан Форте); *S.Afr.*: Proctosedyl; Reparil; Stibium Comp†; *Singapore*: Erase; Proctosedyl; Reparil-Gel N; *Spain*: Contusin; Essavenon†; Reparil; Urgenin†; Venacol†; *Swed.*: Proctosedyl†; *Switz.*: Augentonicum; Demoven N; DUL-X Cool; Flavovenyl; Flavovenyl; Hametum-N; Ipasin; Lapidar 4; PC 30 V; Reparil N; Suppositoires contre les hemorroides; Venaphyt N; *Thai.*: Essaven; Proctosedyl; Reparil; Veno-Gel†; *Turk.*: Prepagel; *Ukr.*: Aescusan (Эскузан); Eskuvit (Эскувит); Fitoval Lotion (Фитовал Лосьон); Herbion Aesculus (Гербион Эскулус); Proctosedyl (Проктоседил); Reparil-Gel N (Репарил-Гель Н); Venen Theiss (Венен Тайсс); Venitan Forte (Венитан); Venosan (Веносан); *USA*: Bioflex; Flexgen; *Venez.*: Gelsem.

Homoeopathic Preparations. *Austria*: Haemex; Venodril; Vensa; Wirbelsaule- und Gelenkstropfen Nr 2†; *Canad.*: Avenoc†; Cutisitum†; Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; Hae 2 Complex†; Hylands Hemorrhoids; *Chile*: Calcarea fluor Compuesta; Variplant; Variplex; *Fr.*: Abbe Chaupitre no 15†; Abbe Chaupitre no 64†; Aesculus Complexe No 103; Aesculus Compose; Avenoc; Boripharm No 1†; Hamamelis Compose; Homeodose 20†; Sepia Compose; Vascoflor; Veinosium†; *Ger.*: Conisan A†; Conisan B†; Conjunctisan-AN†; Conjunctisan-BN†; Haemorrhoid-Gastreu N; Heweven Complex; Neuri-cyl N Ho-Len-Complex; Phonix Silybum spag; phono Ven; Reproven N; Rheuma-Hevert†; Secale-Gastreu; Secalosan N; Varicylum N; Venen-Komplex Ho-Pu-Complex; Veno-Injektopas; veno-loges N; Venokatt; Venoselect N; Wibotin HM; *Neth.*: Achilite; Acidolite; Aesculus Comp; Ambheel; Homeocare Vasco; Ommilite; Venafleur; *Port.*: Avenoc; *Rus.*: Menalgin (Менальгин); Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Vensa (Венза); *S.Afr.*: Achillea Comp†; *Switz.*: Gastronol; Regenaplex Nr 38b; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 31b; Regenaplex Nr. 31c; Regenaplex Nr. 51c; Regenaplex Nr. 59b; *UK*: Catarrh Cream; Haemorrhoid Cream; Medicinal Gargle.

Afegostat Tartrate *(USAN, rINNM)*

Afegostat Tartrate d'; Afegostat Tartras; AT-2101; HGT-3410; Isofagomine Tartrate; Tartrato de afegostat; Афегостата Тартрат.

(3*R*,4*R*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol hydrogen tartrate.

$C_6H_{13}NO_3.C_4H_6O_6$=297.3

CAS — 169105-89-8 (afegostat); 161302-93-8 (afegostat hydrochloride); 919364-56-0 (afegostat tartrate).

UNII — 285Z19773.

NOTE. The name Plicera has been used as a trade mark for afegostat tartrate. The code AT-2101 has also been applied to a topical formulation of diclofenac in hyaluronic acid used in the treatment of actinic keratoses.

Profile

Afegostat tartrate is an iminosugar under investigation for oral therapy of Gaucher disease (p. 2433.3). It is a pharmacological chaperone that stabilises the variant lysosomal glucocerebrosidase facilitating its folding and transport from the endoplasmic reticulum into lysosomes, thereby increasing the pool of active endogenous enzyme.

Afelimomab *(rINN)*

Afelimomab; Afelimomabum; MAK-195F; Афелимомаб.

Immunoglobulin G3, anti-(human tumor necrosis factor α) F (ab')2 fragment (mouse monoclonal LUS4107 γ3-chain), disulfide with mouse monoclonal LUS4107 κ-chain, dimer.

CAS — 156277-98-4.

ATC — L04AB03.

ATC Vet — QL04AB03.

NOTE. The name Segard has been used as a trade mark for afelimomab.

Profile

Afelimomab is a monoclonal tumour necrosis factor antibody that has been investigated for the treatment of sepsis.

References.

1. Vincent JL. Afelimomab. *Int J Clin Pract* 2000; 54: 190–3.
2. Reinhart K, *et al.* Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES study. *Crit Care Med* 2001; 29: 765–9.
3. Gallagher J, *et al.* A multicenter, open-label, prospective, randomized, dose-ranging pharmacokinetic study of the anti-TNF-alpha antibody afelimomab in patients with sepsis syndrome. *Intensive Care Med.* 2001; 27: 1169–78.
4. Panacek EA, *et al.* Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004; 32: 2173–82.

Aflatoxins

Aflatoxins.

CAS — 1162-65-8 (aflatoxin B_1); 7220-81-7 (aflatoxin B_2); 1165-39-5 (aflatoxin G_1); 7241-98-7 (aflatoxin G_2); 6795-23-9 (aflatoxin M_1); 6885-57-0 (aflatoxin M_2).

Profile

Aflatoxins are toxic metabolites produced by many strains of *Aspergillus flavus* and *A. parasiticus*, growing on many vegetable foods, notably maize and peanuts. Several forms, including aflatoxins B_1, B_2, G_1, and G_2 have been identified. Aflatoxins M_1 and M_2 are metabolites produced by *animals* after ingestion of aflatoxins B_1 and B_2; they may be detected in cows' milk.

Aflatoxins can cause hepatitis and cirrhosis. They have been implicated in liver cancer, and may act as co-carcinogens with hepatitis B virus. Aflatoxin B_1 is reported to be one of the most potent carcinogens known in *animals*. It has been reported that aflatoxins have been developed in some countries as biological weapons.

References.

1. Ross RK, *et al.* Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992; 339: 943–6.
2. Jackson PE, Groopman JD. Aflatoxin and liver cancer. *Baillieres Best Pract Res Clin Gastroenterol* 1999; 13: 545–55.
3. Peraica M, *et al.* Toxic effects of mycotoxins in humans. *Bull WHO* 1999; 77: 754–66.
4. Pitt JI. Toxigenic fungi and mycotoxins. *Br Med Bull* 2000; 56: 184–92.

Agnus Castus ⊗

Agni Casti; Agni Casti Fructus; Agnocasto; Chaste Tree Fruit; Chasteberry; Drmkový plod; Gattiller, fruit de; Keuschlamm; Mönchspfeffer; Monk's Pepper; Munkpeppar; Owoc niepokalanka zwyczajnego; Sauzgatillo; Siveydenpuunhedelmä; Zerolo; Монаший Перец.

ATC — G02CX03.

ATC Vet — QG02CX03.

ATC Herb — HG02WX5005 (Vitex agnus-castus: fruit).

UNII — 433OSF3U8A.

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

Ph. Eur. 8: (Agnus Castus Fruit). The whole, ripe, dried fruit of *Vitex agnus castus*. It contains a minimum 0.08% of casticin calculated with reference to the dried drug. Protect from light.

USP 36: (Chaste Tree). The dried ripe fruits of *Vitex agnus-castus* (Verbenaceae). It contains not less than 0.05% of agnuside and not less than 0.08% of casticin, calculated on the dried basis.

Uses and Administration

Agnus castus is reported to affect the secretion of luteinising hormone, follicle stimulating hormone, and prolactin by the pituitary. Both inhibition and stimulation of prolactin secretion have been reported, and may be dose-dependent. Agnus castus is included in herbal preparations for the symptoms of premenstrual syndrome, including mastalgia; it has also been used for menstrual cycle irregularities or menopausal disorders, but should be avoided in patients receiving exogenous sex hormones, including oral contraceptives.

Homoeopathy

Agnus castus has been used in homoeopathic medicines under the following names: Vitex agnus-castus; Agn. cast.; Agnus.

References.

1. Houghton P. Agnus castus. *Pharm J* 1994; 253: 720–1.
2. Christie S, Walker AF. Vitex agnus-castus L.: (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. *Eur J Herbal Med* 1997; 3: 29–45.
3. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; 322: 134–7.
4. Chrubasik S, Roufogalis BD. Chaste tree fruit for female disorders. *Aust J Pharm* 2001; 82: 156–7.
5. Wuttke W, *et al.* Chaste tree (Vitex agnus-castus)—pharmacology and clinical indications. *Phytomedicine* 2003; 10: 348–57.
6. Döll M. Das prämenstruelle Syndrom: Wirksamkeit von Vitex agnus castus. *Med Monatsschr Pharm* 2009; 32: 186–91.
7. van Die MD, *et al.* *Vitex agnus-castus* (Chaste-Tree/Berry) in the treatment of menopause-related complaints. *J Altern Complement Med* 2009; 15: 853–62.

Adverse Effects and Precautions

The adverse effects of agnus castus are reported to be mild and reversible, with acne, erythematous rash, headache, gastrointestinal disorders, menstrual disorders, nausea, and pruritus being the most frequently reported.[1] Toxicity data for use of agnus castus during pregnancy and breast feeding are sparse and its safety is therefore unclear.[1,2] In view of its pharmacological actions, use is not recommended.[1] There is a theoretical possibility of drug interactions between agnus castus and dopamine antagonists.[1]

1. Daniele C, *et al.* Vitex agnus castus: a systematic review of adverse events. *Drug Safety* 2005; 28: 319–32.
2. Dugoua J-J, *et al.* Safety and efficacy of chastetree (*Vitex agnus-castus*) during pregnancy and lactation. *Can J Clin Pharmacol* 2008; 15: e74–e79.

Interactions

For reference to potential interactions with agnus castus and dopamine antagonists, see above. For a suggestion of a potential interaction between agnus castus and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Premular; *Austria*: Agnofem; Agnucaston; Agnumens†; *Braz.*: Lutene†; Nalte; Tenag; Vitenon; Vitex; *Chile*: Dimenox; *Cz.*: Agnucaston; Cesnafemme†; *Ger.*: Agnolyt; Agnucaston; Agnus; Biofem†; Castuvemin; Cefanorm†; Femicur N; Feminon A; Femisana mens†; Gynocastus; Sarai†; Strotan; Agnucaston; Cefanorm; PreMens; *Indon.*: Agnu Gyne†; Agnucaston†; *Mex.*: Ciclo-plant†; *Norw.*: Femicur†; *Pol.*: Agufem; Castagnus; Cyclocynon; Feminon PMS; *Rus.*: Agnucaston (Агнукастон); Cyclodynon (Циклодинон); *Spain*: Dismegyn; Femiplante†; *Swed.*: Femicur; *Switz.*: Cyclodynon†; Oprane; Prefemine; PreMens; *Turk.*: Agnucaston; Biofem†; *UK*: Cyclopret; Herbal Premens; Kira Prem; Periagna; Premherb; *Ukr.*: Cyclodynon (Циклодинон).

Multi-ingredient Preparations. *Austral.*: Dong Quai Complex†; Extralife Meno-Care†; Extralife PMS-Care†; Femi-Nan; Feminine Herbal Complex; Femme-F; PM H-Regulator; PM LifeFro Max for Women; PMT-Eze†; Prosense for Women†; *Canad.*: Natural HRT; Phytoestrin; *Hong Kong*: Phytoestrin†; *India*: Evepearl-PMS; *Indon.*: Herbalacta†; *Ital.*: Bioestril Ginseng; Bioestril Valeriana; Climil Complex; Climil-80; Ginecast; Spa-OK; *Singapore*: Phytoestrin†; *UK*: Flash Fighters; *Ukr.*: Evita (Евита)†.

Homoeopathic Preparations. *Austria*: Erbiode-Starkungstropfen; Mastodynon; Pascofemin; *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Amphosca†; Ervopax†; Fatigue; Homeo-Form F†; *Cz.*: Mastodynon; *Fr.*: Agnus Castus Complexe No 2†; Amphosca Orchitine; Amphosca Ovarine; Boripharm No 31; Nervopax; *Ger.*: Agnurell; Agnus castus comp†; Agnus femin; Antimast†; Antimast TN†; Bomaklim; Emasex-A vitex; Feminon N; Klimaktosin; Mastodynon; Pascofemin; Phyto-L; Viragil; Viril s-Gastreu S R41; *Neth.*: Emvita 10; Homeocare Cyclo; Mastodynon†; Mulimen H; *Rus.*: Damiana-Plus (Дамиана-Плюс); Dysmenorm (Дисменорм); Mastodynon (Мастодинон); *Switz.*: Menosant†; *Thai.*: Mastodynon†; *Ukr.*: Dysmenorm (Дисменорм.); Mastodynon (Мастодинон).

Agrimony

Agrimoña; Agrimonia; Agrimoniae Herba; Aigremoine; Cafetí; Dirvuolių žolė; Hierba bacera; Hierba de San Guillermo; Hierba del podador; Maarianverijuuri; Odermennigkraut; Párlófű; Småborre; Řepíková nať; Пенешок Аптечный.

ATC Herb — HA01WA5001 (Agrimonia eupatoria: herb); HD02WX5001 (Agrimonia eupatoria: herb).

UNII — EBU0U94820 (Agrimonia eupatoria); GYD07VBS73 (Agrimonia eupatoria flowering top).

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

Ph. Eur. 8: (Agrimony). The dried flowering tops of *Agrimonia eupatoria* containing a minimum of 2.0% of tannins expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Agrimony, the aerial parts of *Agrimonia eupatoria* (Rosaceae) or more rarely *A. procera* (*A. odorata*; fragrant agrimony), has astringent and diuretic properties. It is used internally for diarrhoea, biliary and other gastrointestinal disorders, and

urinary-tract disorders; it has also been used for inflammatory mouth and throat disorders. It has been used externally for wound healing and skin disorders.

A. pilosa is used in traditional Chinese medicine. It contains the tannin agrimoniin which is reported to be an inducer of interleukin-1 production.

Homoeopathy

Agrimony has been used in homoeopathic medicines under the following names: Agrimonia eupatoria; Agrimonia eup; Agrimonia eupatoria, flos; Agrimonia eup, flos; Agrimonia odorata, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Repíkovy Caj, Repíkova Nat.

Multi-ingredient Preparations. *Austral.*: Detox Program; Digestive Bitters; *Austria*: Amersan; Gallen- und Leberteé St Severin; *Cz.*: Amersan; Herbadent; Species Cholagogae Planta†; Stomaran; The Salvat; Zlucnikova Cajova Smes; *Fr.*: Tisane Hepatique de Hoerdt†; *Hung.*: Majvedo es Detoxikalo; Urogin; Vesevedo; *Rus.*: Herbion Drops for the Gallbladder (Ербион Капли Желчегонные)†; *Switz.*: Kernosan 24; *UK*: Piletabs; *Ukr.*: Herbion Drops for the Gallbladder (Ербион Капли Желчегонные).

Homoeopathic Preparations. *Fr.*: Poconeol no 57; Poconeol no 81†; *Switz.*: Regenaplex Nr. 25b; Regenaplex Nr. 35b; Regenaplex Nr. 79; Regenaplex Nr. 80aN.

Alfalfa

Alfaz; Luceme; Mielga; Purple medick; Люцерна.
CAS — 543-38-4 (canavanine).
ATC - Herb — HG04BW5022 (Medicago sativa herb); HA10BX5004 (Medicago sativa herb).
UNII — SQ2N8Y9KR (alfalfa top); HY3L927V6M (alfalfa leaf); DJC934BRBD (alfalfa).

Pharmacopoeias. *Br.* includes a form for homoeopathic preparations.

BP 2014: (Medicago Sativa for Homoeopathic Preparations). The fresh whole flowering plant of *Medicago sativa*.

Profile

Alfalfa is the plant *Medicago sativa* (Leguminosae) which is cultivated as an animal feedstuff. The seeds and sprouts of alfalfa contain canavanine (2-amino-4-(guanidinooxy) butyric acid), a toxic amino acid structurally related to arginine; content is reported to represent about 1.5% of the dry weight. A syndrome resembling SLE has been recorded in *monkeys* fed alfalfa.

Alfalfa is used in herbal preparations for a variety of disorders.

Homoeopathy

Alfalfa has been used in homoeopathic medicines under the following names: Alfa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Esterin.

Multi-ingredient Preparations. *Arg.*: Calmag D; Daily Nutrilite; *Austral.*: Irontona†; Vitatona†; *Chile*: Calcio 520; *Fr.*: Gonaxine; *Ukr.*: Alfagin (Алфагин).

Homoeopathic Preparations. *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Alfalfa Tonic Comp-Drops 1 Stress†; Fatigue; Homeo-Form F†; Homeo-Form P†; Motherwort Combination 3†; *Fr.*: Soreal; *Switz.*: Nelsons Noctura†; *UK*: Noctura.

Alfaprostol *(BAN, USAN, rINN)*

Alfaprostolum; K-11941; Ro-22-9000; Альфапростон.
Methyl (Z)-7-[(1*R*,2*S*,3*R*,5*S*)-2-[(3*S*)-5-cyclohexyl-3-hydroxypent-1-ynyl]-3,5-dihydroxycyclopentyl]hept-5-enoate.
$C_{24}H_{38}O_5$=406.6
CAS — 74176-31-1.
ATC Vet — QG02AD94.
UNII — 4XKL2U08L.

Profile

Alfaprostol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Alglucerase *(BAN, USAN, rINN)*

Alglucerasa; Alglucérase; Alglucerasum; Glucosylceramidase; Macrophage-targeted β-Glucocerebrosidase; Алглюцераза.
CAS — 143003-46-7.
ATC — A16AB01.
ATC Vet — QA16AB01.
UNII — 27T56C7KK0.

Description. Alglucerase is a modified form of human placental β-glucocerebrosidase (ceramide glucosidase; β-D-glucosyl-*N*-acylsphingosine glucohydrolase). It is a monomeric glycoprotein of 497 amino acids with glycosylation making up about 6% of the molecule.

Imiglucerase *(BAN, USAN, rINN)*

Imiglucerasa; Imiglucérase; Imiglucerasum; Imiglukeraasi; Imiglukeras; Imigluseraz; r-GCR; Recombinant Macrophage-targeted β-Glucocerebrosidase; Имиглюцераза.
CAS — 154248-97-2.
ATC — A16AB02.
ATC Vet — QA16AB02.
UNII — Q6U6J488WY.

Description. Imiglucerase is a recombinant modified form of human β-glucocerebrosidase. It is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites. Imiglucerase differs from placental glucocerebrosidase by 1 amino acid at position 495, where histidine is substituted for arginine.

Taliglucerase Alfa *(USAN, rINN)*

prGCD; Taliglucerasa Alfa; Taliglucérase Alfa; Taliglucerasum Alfa; Талиглюцераза Альфа.
CAS — 37228-64-1.
ATC — A16AB11.
ATC Vet — QA16AB11.
UNII — 0R4NLX88O4.

Description. Taliglucerase alfa is a recombinant modified form of human β-glucocerebrosidase. It is a monomeric glycoprotein containing 4 N-linked glycosylation sites. Taliglucerase alfa differs from human glucocerebrosidase by 2 amino acids at the *N*-terminal and up to 7 amino acids at the C-terminal.

The name Uplyso has been used as a trade mark for taliglucerase alfa.

Velaglucerase Alfa *(BAN, USAN, rINN)*

Velaglucerasa alfa; Velaglucérase alfa; Velaglucerasum alfa; Велаглюцераза Альфа.
CAS — 884604-91-5.
ATC — A16AB10.
ATC Vet — QA16AB10.
UNII — 23HYE3680L.

Description. Velaglucerase alfa is produced by gene activation technology in a human cell line and has the same amino acid sequence as human glucocerebrosidase. It contains 5 potential N-linked glycosylation sites, 4 of which are occupied by glycan chains.

Uses and Administration

The enzyme β-glucocerebrosidase is given as imiglucerase, taliglucerase alfa, velaglucerase alfa, or occasionally alglucerase for long-term enzyme replacement therapy in patients with Gaucher disease (see below). The oligosaccharide chains of the enzyme are modified to terminate with mannose residues to ensure uptake into macrophages.

Alglucerase, imiglucerase, taliglucerase alfa, and velaglucerase alfa are used in the management of type 1 Gaucher disease; imiglucerase may also be used in patients with type 3 who have clinically significant non-neurological manifestations of the disease. The usual dose for each of these is 60 units/kg given once every 2 weeks by intravenous infusion over 1 to 2 hours. The solution should be filtered through a low-protein-binding 0.2 micrometre in-line filter during administration. The dose should be individualised according to disease severity and adjusted according to response. Doses ranging as low as 15 units/kg once every 2 weeks have been used, and initial doses of imiglucerase 2.5 units/kg given 3 times weekly have been reported.

For administration in children, see below.

Reviews.

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3. Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. *Drug Des Devel Ther* 2012; 6: 81–106.
4. Hollak CEM. An evidence-based review of the potential benefits of taliglucerase alfa in the treatment of patients with Gaucher disease. *Curr Med* 2012; 7: 15–20.

Administration in children. Alglucerase, imiglucerase, and velaglucerase alfa may be given to children in the same dosing regimen as that usually used in adults (see above). However, licensed product information states that safety and efficacy have not been established for alglucerase and imiglucerase in children younger than 2 years of age, or for velaglucerase alfa in those aged less than 4 years.

The *BNFC* suggests that imiglucerase may be used similarly in neonates and infants, and that doses up to 120 units/kg once every 2 weeks by intravenous infusion may be given to patients with type 3 Gaucher disease.

Gaucher disease. Gaucher disease (glucocerebrosidosis) is a rare, autosomal recessive disorder, although it is the commonest lysosomal storage disorder. It is caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase (acid β-glucosidase, ceramide glucosidase, β-D-glucosyl-*N*-acylsphingosine glucohydrolase, or glucosylceramidase) which catalyses the hydrolysis of glucocerebroside, a lipid component of cell membranes, to glucose and ceramide. Deficiency of β-glucocerebrosidase results in accumulation of glucocerebroside in the lysosomes of reticuloendothelial cells, particularly macrophages.[1-3]

Gaucher disease is classified into three main forms based on clinical signs and symptoms. Hepatosplenomegaly occurs in all forms. Type 1 Gaucher disease (chronic adult non-neuronopathic disease) accounts for 90% or more of cases and occurs especially in Ashkenazi Jews. More than half of all patients with type 1 disease are diagnosed before the age of 10 years.[4] The disease follows a chronic course of variable severity and onset, with hepatosplenomegaly and blood and bone disorders being the main features; there is no neurological involvement. In type 2 Gaucher disease (acute infantile neuronopathic disease), neurological involvement predominates. Patients show developmental delay by the age of 6 months, suffer seizures, pulmonary infections, and usually die in early childhood. Type 3 Gaucher disease is a subacute neuronopathic form and is slowly progressive.[4] There are 3 subtypes varying in severity and prognosis: in type 3a, there is slow progressive neurological deterioration with death usually occurring during childhood; in type 3b (Norrbotten disease) there is slow cognitive deterioration and patients may survive to adulthood; type 3c typically affects patients of Palestinian, Arab, or Japanese descent, with possible survival to the teenage years.

Treatment of Gaucher disease was previously limited to symptomatic management until the development of enzyme replacement therapy with β-glucocerebrosidase. Due to the rarity of Gaucher disease, early clinical studies were limited mainly to small case series of patients with type 1 disease. β-Glucocerebrosidase is given as imiglucerase or velaglucerase alfa, or occasionally as alglucerase or taliglucerase alfa. Use of such therapy has been shown to reverse hepatosplenomegaly and the haematological abnormalities;[7,8] effects may be seen within a few months, although in many the response is poor during the first 6 to 9 months and then improves rapidly.[2] Return to normal haemoglobin values within 6 to 12 months has been reported, as has reduction in liver size by 20 to 30% within 2 years and 30 to 40% by 5 years; a 50% reduction in spleen size also occurred.[9] Bone symptoms respond more slowly. Decreases in bone pain during the first year of treatment have been reported although there was no radiological improvement.[8] Existing bone manifestations are slow to respond or refractory to enzyme replacement therapy, but alendronate has been shown to be of benefit as adjunctive therapy for osteopenia in 36 adults with negative lumbar bone mineral density scores who had been receiving glucocerebrosidase for at least 2 years.[10] Normalised growth velocity has been reported in children[11] and radiographical assessments have shown improvements in bone density and mineralisation.[12] There is evidence that long-term enzyme replacement therapy for up to 8 years completely or partially ameliorates anaemia, thrombocytopenia, organomegaly, and bone pain in patients with type 1 Gaucher disease, as well as preventing further deterioration.[9,13] However, successful symptom control is dependent on the degree of damage that has already occurred, and early initiation of therapy is recommended for a more favourable prognosis.[3,14] Enzyme replacement therapy in Gaucher disease is lifelong and relapses occur with prolonged interruptions to therapy.[6,15] Taliglucerase alfa[16] and velaglucerase alfa[17] are used similarly to imiglucerase in the treatment of type 1 Gaucher disease. Alglucerase has also been tried in rare cases of Gaucher disease affecting the heart[18] or the eye.[19] It is not yet known whether enzyme replacement therapy is able to prevent the development of symptoms in asymptomatic patients.

The efficacy of enzyme replacement therapy in managing neurological symptoms in patients with type 2 or type 3 disease[20] is unproven. Most of the patients with type 3 Gaucher disease in a small study[21] did not deteriorate neurologically when treated with doses that reversed almost all the systemic manifestations. However, it was pointed out that the amount of enzyme that crosses the blood-brain barrier is unlikely to be significant, and other forms of treatment specifically for neuronopathic Gaucher disease need to be developed.

For those patients with type 1 Gaucher disease in whom enzyme replacement therapy may be unsuitable, miglustat may be used. It reduces the synthesis of glucocerebroside by inhibiting glucosyltransferase, one of the early enzymes in the sphingolipid biosynthetic pathway. However, the balance of benefits versus adverse affects with miglustat is less favourable than with imiglucerase, which remains the standard treatment where possible; the two drugs should not be used together.[22]

Haematopoietic stem cell transplantation has produced favourable outcomes in patients with Gaucher disease and could potentially provide a permanent cure. However, the procedure is not without risk of death or significant morbidity, and until these are reduced to an acceptable level by further technological advances supported by data from good clinical studies, it is reserved as a late treatment option, by which time a complete cure is less likely.[23]

Possible future therapies under investigation for Gaucher disease include oral therapy with the pharmacological chaperone afegostat tartrate, and gene therapy. Other modified forms of β-glucocerebrosidase are also under investigation to improve uptake into the affected macrophages.

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Adverse Effects and Precautions

Reactions occurring during or shortly after infusion of alglucerase, imiglucerase, taliglucerase alfa, or velaglucerase alfa can include fever, chills, pruritus, flushing, and gastrointestinal symptoms including cramps, diarrhoea, nausea, and vomiting. Some of these may be hypersensitivity reactions; other hypersensitivity reactions, including urticaria and angioedema, respiratory symptoms, and hypotension have also occurred. Anaphylactoid reactions have occurred rarely with imiglucerase and taliglucerase alfa. Caution is required in patients who have shown signs of hypersensitivity; reduction of the rate of infusion, and pretreatment with antihistamines and/or corticosteroids may permit further treatment. Antibodies have developed in about 15% of patients during the first year of therapy with alglucerase or imiglucerase. The development of antibodies to taliglucerase alfa and velaglucerase alfa has also been reported. Patients who develop antibodies are at increased risk of hypersensitivity reactions and periodic assessment for antibody formation is recommended.

Pain and irritation at the injection site may occur. Other adverse effects reported include fatigue, dizziness, headache, backache, peripheral oedema, mouth ulcers, and disturbances in sense of smell.

Alglucerase is prepared from human placentas and its infusion therefore carries a risk of transmission of infections although this is minimised by the manufacturing process. Chorionic gonadotrophin, a naturally occurring hormone in human placentas, has been detected in alglucerase. The presence of this hormone may produce early virilisation in young boys if sufficient is given, and has the potential to produce false positive results in pregnancy tests that rely on the detection of this hormone. Alglucerase should be used with caution, if at all, in patients with androgen-sensitive malignancies.

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Effects on the lungs. Pulmonary hypertension developed in 2 patients with Gaucher disease after starting treatment with alglucerase.[1] Neither patient had evidence of parenchymal lung infiltration with Gaucher cells.

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Pharmacokinetics

After intravenous infusion, plasma enzymatic activities of alglucerase and imiglucerase decline rapidly from steady state, with an elimination half-life of between 3.6 and 10.4 minutes. Taliglucerase alfa is cleared with a terminal half-life of 18.9 to 28.7 minutes, and velaglucerase alfa has a half-life of 5 to 12 minutes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cerezyme; ***Austria***: Cerezyme; ***Belg.***: Cerezyme; ***Braz.***: Cerezyme; ***Canad.***: Cerezyme; ***Chile***: Cerezyme; ***China***: Cerezyme (思而赞); ***Cz.***: Cerezyme; ***Denm.***: Cerezyme; VPRIV; ***Fin.***: Cerezyme; ***Fr.***: Cerezyme; VPRIV; ***Ger.***: Cerezyme; VPRIV; ***Gr.***: Cerezyme; ***Hong Kong***: Cerezyme; ***Irl.***: Cerezyme; VPRIV; ***Israel***: Cerezyme; Elelyso; VPRIV; ***Ital.***: Cerezyme; ***Jpn***: Cerezyme; ***Malaysia***: Cerezyme; ***Neth.***: Cerezyme; VPRIV; ***Norw.***: Cerezyme; VPRIV; ***NZ***: Cerezyme; ***Pol.***: Cerezyme; VPRIV; ***Port.***: Cerezyme; VPRIV; ***Rus.***: Cerezyme (Церезим); ***S.Afr.***: Cerezyme; ***Spain***: Cerezyme; Vpriv; ***Swed.***: Cerezyme; VPRIV; ***Switz.***: Cerezyme; ***Thai.***: Cerezyme; ***Turk.***: Cerezyme; ***UK***: Cerezyme; VPRIV; ***Ukr.***: Cerezyme (Церезим); ***USA***: Ceredase†; Cerezyme; Elelyso; VPRIV.

Alibendol *(rINN)*

Alibendolum; Алибендол.

5-Allyl-*N*-(2-hydroxyethyl)-3-methoxysalicylamide.

$C_{13}H_{17}NO_4$=251.3

CAS — 26750-81-2.

UNII — A8CO1VZK2Z.

Profile

Alibendol is a choleretic used in the treatment of gastrointestinal disorders.

Alipogene Tiparvovec *(rINN)*

AAV1-LPL^{S447X}; Alipogen tiparvovec; Alipogène tiparvovec; Alipogenum tiparvovecum; AMT-011; Алипоген Типарвовек.

Recombinant adeno-associated virus serotype 1 (AAV1) vector expressing the S447X variant of the human lipoprotein lipase (LPL) gene.

CAS — 929881-05-0.

ATC — C10AX10.

ATC Vet — QC10AX10.

Profile

Alipogene tiparvovec is a gene therapy product (p. 2511.2) used in the treatment of adult patients with familial lipoprotein lipase (LPL) deficiency who have severe or recurrent pancreatitis. It is made from a nonreplicating adeno-associated viral vector (AAV1) that carries a gene for LPL. Alipogene tiparvovec is licensed for use as a single injection series, using a solution that contains 3×10^{12} genome copies per mL. The maximum total dose is 1×10^{12}/kg. Multiple injections should be made intramuscularly into the legs and the use of spinal or regional anaesthesia is advised; the recommended dose per injection site is 1.5×10^{12}.

For 3 days before, and for 12 weeks after, treatment, immunosuppressive therapy should be given: ciclosporin (3 mg/kg daily) and mycophenolate mofetil (2 g daily) have been suggested. In addition, an intravenous dose of methylprednisolone (1 mg/kg) should be given 30 minutes before starting treatment.

It is also under investigation for the treatment of type V hyperlipoproteinaemia, syndrome X, and non-alcoholic steatohepatitis.

References.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Neth.***: Glybera.

Allergen Products

Alergenos; Allergeenivalmisteet; Allergenprodukter; Producta Allergenica; Produits allergènes.

Uses and Administration

Allergen products are used diagnostically in skin tests and provocation tests to confirm the cause of a suspected hypersensitivity reaction. They are also used for allergen immunotherapy in certain patients with hypersensitivity reactions, particularly to insect venoms such as bee or wasp venom, pollen (p. 2593.3), house dust, and house-dust mite. Preparations for allergen immunotherapy are given by subcutaneous injection or sublingually. Other routes (such as oral, nasal, or bronchial) have also been tried.

Administration. Allergen vaccines used for allergen immunotherapy (see p. 2435.1) should be well characterised and standardised for total allergenic potency, biological activity, and shelf-life. Whenever possible, the same batch of allergen should be used during a course of treatment because of possible differences in potency between batches. Injections for allergen immunotherapy are given subcutaneously as aqueous extracts or combined with adjuvants to reduce adverse effects while retaining or enhancing immunogenicity. Such modified vaccines are slow-release formulations and therefore the interval between injections is increased. Vaccines can be physically modified by adsorption onto an inert carrier such as aluminium or calcium salts, or tyrosine, or chemically modified with glutaral, formaldehyde, or liposomes. Combinations of the two types of modified vaccine may also be used.

Dosage regimens for allergen immunotherapy are as recommended by the manufacturers and depend on the sensitivity of the patient. During the initial build-up phase, the dose of allergen vaccine is slowly increased (by increasing the concentration and/or the dose volume) until the maintenance dose is reached. However, the dose should be reduced after a systemic reaction, or stopped if the reaction is severe. Likewise, the dose might need to be reduced or not given at all to highly sensitised patients during periods of natural exposure to the allergen.

In *conventional* build-up schedules, injections of aqueous extracts are given once or twice weekly, with maintenance expected to be reached in 4 to 6 months. Depot preparations are given every 1 to 2 weeks. *Modified dosage schedules* have been used where maintenance needs to be achieved more quickly; such regimens may, however, be associated with an increased risk of adverse reactions, although this can be ameliorated by premedication with an antihistamine. Aqueous extracts should be used for modified schedules until the maintenance dose is reached. In *cluster schedules* several injections may be given on the same day, usually at 30-minute intervals, once or twice a week on non-consecutive days. Fewer total injections are used than with conventional schedules and maintenance therapy can be reached in as little as 4 weeks. There might be a slight increase in risk of systemic reactions. *Rush schedules* are more rapid than cluster schedules and several injections are given at specified intervals once daily on consecutive days allowing maintenance doses to be reached in a matter of days; naturally, this does increase the risk of systemic adverse effects and patients need to be monitored more closely and for longer than with conventional schedules. *Ultrarush schedules* are even faster and may be used to accelerate desensitisation to stinging insects in highly sensitive individuals. When the maintenance dose has been

reached, the injection interval is progressively increased as necessary according to safety and efficacy. Injection intervals are typically 2 to 4 weeks for aeroallergens and 8 weeks for insect venom. The optimal duration of allergen immunotherapy is unknown, but a period of 3 to 5 years is usually recommended; the decision to discontinue therapy will depend on individual response. Some patients will remain desensitised after stopping allergen immunotherapy but others will relapse.

The sublingual route is also used for allergen immunotherapy, with the vaccine given daily either as a solution or as oral lyophilisate tablets. It is considered to be a good alternative to the subcutaneous route in terms of safety and efficacy, although the optimal vaccine dose in relation to efficacy and duration of treatment is still undetermined. The oral, nasal, and bronchial routes have also been tried for allergen immunotherapy, although efficacy or safety has not always been shown.

Modification of allergens is being investigated as an alternative way to increase safety and efficacy, and developments include recombinant proteins, peptides, plasmid DNA vaccines, and immunostimulatory sequences of DNA conjugated to specific allergens. Other immunomodulatory methods include use of allergen-specific antibodies or fragments, and humanised anti-IgE monoclonal antibodies (e.g. omalizumab, p. 1216.3). Also, more efficient adjuvants such as monophosphoryl lipid A are being tried.

References.

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Allergen immunotherapy. Allergic reactions are type I (immediate) hypersensitivity reactions mediated by IgE antibodies (see under Hypersensitivity, p. 610.1) that are usually managed by anti-allergic medication or, where possible, allergen avoidance. For patients in whom these treatment methods are inadequate or unsuitable, allergen immunotherapy (desensitisation or hyposensitisation) may be tried. Specific allergen immunotherapy (SIT) is the administration of gradually increasing quantities of an allergen vaccine to a patient with diagnosed IgE-mediated allergy until a maintenance dose is reached that is effective in ameliorating symptoms associated with subsequent exposure to the allergen.[1-4] The mechanism of action is thought to be through T-helper (Th) cell switching by rectifying the balance between Th1 and Th2 lymphocytes and increasing the levels of protective IgG while decreasing the levels of IgE.[2,4-6] Long-lasting benefit is conferred, and the quality of life improved in patients for whom allergen avoidance is difficult or impossible. Patients must have demonstrable evidence of specific IgE antibodies before undergoing allergen immunotherapy (see Diagnostic Use below), and it is generally recommended that diagnosis of allergies and allergen immunotherapy should only be carried out in specialist centres. Subcutaneous injection immunotherapy (SCIT) is the traditional method of administration and has a long history of use. Sublingual immunotherapy (SLIT) is now also widely used, and other routes have been tried—see Administration, p. 2434.3. Reports of severe and sometimes fatal hypersensitivity reactions to injected allergen preparations prompted recommendations to reduce the risk of systemic reactions (see under Adverse Effects, p. 2436.2).

The use of allergen immunotherapy has been reviewed[4,7] and recommendations have been published.[2,3,8,9] The incidence and severity of allergic disease is increasing as a result of environmental changes, and allergies represent a major cause of illness in developed countries; in the UK for example, they are estimated to affect 1 in 3 people. Of particular concern is the rise in multi-system allergies.[4] Common sources of allergens include: pollen and fungal spores producing seasonal allergic rhinitis and conjunctivitis (hay fever); house dust, house-dust mites, and animal dander producing perennial allergic rhinitis; venom from bees, wasps, and stinging ants; latex rubber, flour, and other allergens giving rise to occupational rhinitis; drugs (e.g. penicillins, anaesthetics); and some foods (e.g. nuts, shellfish).[4] Allergic reactions are a common cause of childhood asthma and are also associated with atopic eczema.[4]

Not all allergies are suitable for treatment with specific allergen immunotherapy and recommendations made by the CSM[10] in the UK are that allergen immunotherapy should only be used for seasonal allergic rhinitis (hay fever) in patients not responsive to anti-allergic drugs, and for hypersensitivity to bee and wasp venoms; warnings against use in patients with asthma are also given (although allergen immunotherapy is used in some countries for the treatment of allergic asthma—see below). The UK CSM[10] also concludes that there is inadequate evidence of benefit from desensitisation to allergens such as house dust, house-dust mites, animal dander, and foods, and therefore does not recommend allergen immunotherapy in these cases.

Allergen immunotherapy is used in children and is thought to be more effective than in adults.[2] It has been suggested that its use in children with allergic rhinoconjunctivitis may also prevent the development of asthma.[3] Review of controlled studies and meta-analyses[11] confirmed that allergen injection immunotherapy is effective in allergic asthma in children, and early intervention may prevent progression to multiple allergen hypersensitivity. However, since adverse effects of allergen immunotherapy are more likely in asthmatics, it is contra-indicated in unstable asthma (see also below). Therapy is generally not recommended for children younger than 5 or 6 years of age[2,3,8] because it is less well tolerated, cooperation with a young child might be difficult,[3] and in this age group the differential diagnosis between allergic rhinitis and viral infection of the respiratory tract may not be clear.[2]

Allergen immunotherapy for seasonal allergic rhinitis and conjunctivitis triggered by pollen has generally been reserved for severely affected patients when anti-allergic drugs have failed.[2,3,8] A systematic review[5] of controlled studies concluded that there is a significant reduction in symptoms and use of medication in suitably selected patients who have not responded adequately to anti-allergic drugs, together with a known and relatively low risk of serious adverse effects with no long-term consequences. The sublingual route is a means of ameliorating the severe systemic reactions associated with injection immunotherapy, and it also offers a more convenient form of dosing.[12] A systematic review[6] of studies using sublingual immunotherapy in patients with seasonal and perennial allergic rhinitis supported the promotion of this route because rhinitis symptoms and use of anti-allergic medication were reduced significantly in adults and no systemic adverse effects were reported. However, it was difficult to assess the magnitude of the effect and compare this route with injection immunotherapy. The treatment effect in children was not significant. However, a meta-analysis[13] of more controlled studies involving a greater total number of children concluded that sublingual immunotherapy was effective in children with allergic rhinitis.

There is some evidence that allergen immunotherapy for allergies such as rhinitis may prevent the development of asthma[3] and thus earlier use may be warranted.[14] A systematic review[15] of randomised controlled studies confirmed that allergen immunotherapy in asthmatic patients reduced the symptoms of asthma and the use of asthma medication, although it was not possible to quantify the benefits compared with other forms of therapy, and the possibility of severe or fatal anaphylaxis remains. Recommendations for the use of allergen immunotherapy in patients with asthma vary. Guidelines issued in the UK[10] in 1994 recommended that asthmatic patients should not be treated with allergen immunotherapy because they are more likely to develop severe adverse effects (although asthma is not considered a contra-indication to allergen immunotherapy for anaphylaxis caused by Hymenoptera spp.). Others,[3,9] including WHO,[2] consider that allergen immunotherapy for allergic rhinoconjunctivitis can be given to patients whose asthma is stable and not severe (FEV_1 is not less than 70% of predicted value),[2] when avoidance of allergens has not been sufficient or is not possible, and drug treatment has failed. Allergen immunotherapy should not be given to patients whose asthma can be controlled by antiasthmatic drugs and allergen avoidance.[16]

Allergen immunotherapy is indicated for patients with specific IgE antibodies who have had severe anaphylaxis after insect stings, particularly those of Hymenoptera (bees, wasps, and stinging ants).[2,3,8,17,18] Vaccines containing purified venom are available for most Hymenoptera spp. and have replaced whole body extract preparations, which were generally found to be ineffective. Venom immunotherapy is very effective in decreasing the risk of systemic reactions to venom in susceptible people.[18] Venom vaccines are not available for stinging ants but whole body extract vaccines may contain sufficient venom antigens to be effective.[2,3,18] Allergen immunotherapy for rhinoconjunctivitis and asthma due to house-dust mite or animal dander can be considered when the allergen is unavoidable.[2,3,9,15] A review[19] considering both injection and sublingual mite immunotherapy in adults and children with asthma and/or rhinitis confirms efficacy, although it is not possible to assess safety relative to other forms of allergen immunotherapy such as pollen vaccines. One multicentre, randomised, dose-response study[20] found that specific mite injection immunotherapy for 1 year improved eczema in patients with atopic dermatitis allergic to house-dust mite. Limited data indicate that allergen immunotherapy might be effective for atopic dermatitis associated with aeroallergen sensitivity.[3] However, more controlled studies are needed to confirm its place in treatment.[4]

Allergen immunotherapy for drug hypersensitivity may be warranted on the rare occasions when continued use is considered essential, possibly with penicillins or insulin.[8,21] In most cases the effect of desensitisation is temporary and if the medication is required again in the future, the process must be repeated.[22]

Allergen immunotherapy has also been tried in other disorders such as urticaria and food allergies, but there is insufficient evidence to support such use[3,4,8,10] and its use is not recommended. The traditional method of allergen immunotherapy in peanut allergy has an unacceptably high rate of systemic adverse reactions and other immunotherapeutic interventions are being sought.[23]

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Diagnostic use. Sensitivity testing can be used to confirm that suspected allergens are mainly responsible for the symptoms of a suspected hypersensitivity reaction. It is

necessary before patients with allergies are managed either by allergen avoidance or treated with allergen immunotherapy (see p. 2435.1). However, sensitivity testing should not form the sole basis of the treatment of hypersensitivity reactions.

Type IV (delayed) hypersensitivity reactions such as contact dermatitis are normally diagnosed using patch tests. Several standard techniques are available, but in general they all involve maintaining a standard amount of the test substance in contact with the skin for 48 to 72 hours. A positive response is shown by erythema, swelling, or vesiculation. The sensitivity of different parts of the body varies, and this should be accounted for in applying test substances and controls. The test results are normally read 30 to 60 minutes after removal of the patches to allow any pressure effects of the patches to subside. Patch testing with mixtures of allergens may be necessary to diagnose contact dermatitis in patients hypersensitive to multiple allergens.

Type I (immediate) hypersensitivity reactions such as allergic rhinitis, allergic asthma, and insect-sting hypersensitivity are tested using skin-prick or intradermal tests. Since the allergen is introduced through the skin in these tests, the risk of systemic reactions is greater than patch testing, and adrenaline injection should be kept available. The skin-prick test involves pricking the epidermis through a drop of allergen in solution, and comparing the result after 15 to 20 minutes with positive and negative controls. This test is inexpensive and the results available rapidly. The intradermal (intracutaneous) test is used if the skin-prick test result does not agree with a strong clinical suspicion, although now that potent allergen extracts are used for skin-prick tests, the intradermal test offers few advantages and has greater risk of systemic reactions. Skin testing is unreliable for evaluating hypersensitivity to drugs, except for penicillins and for certain macromolecules. Skin test titration, that is testing with a series of dilutions, has been used to determine a safe starting dose for allergen immunotherapy.

Provocation tests are designed to reproduce symptoms of hypersensitivity by controlled exposure to a suspected allergen. They are used when skin or laboratory tests are unavailable, or IgE is not involved in the mechanism. Provocation may be by the bronchial, oral, nasal, or ocular routes. Facilities for full cardiopulmonary resuscitation should be immediately available.

In-vitro methods for measuring antigen-specific IgE include immunoassays such as the enzyme-linked immunosorbent assay (ELISA), which has now replaced the radioallergosorbent test (RAST). These tests can be used in place of skin-prick tests but they are expensive and the results not available as quickly.

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Adverse Effects and Treatment

Adverse effects to allergen products can range from mild local reactions to severe generalised reactions that may be fatal, especially reactions to bee and wasp venom. Hypersensitivity reactions may be immediate or delayed.

Adverse effects with **skin-prick testing** are uncommon, although swelling and irritation at the injection site, rhinitis, urticaria, wheezing, and chest tightness might occur, and rarely, anaphylactic shock.

Allergen immunotherapy injections may give rise to swelling, irritation, redness, and hardness at the injection site. Systemic reactions include itching eyes, sneezing, cough, wheezing, chest tightness, atopic eczema, urticaria, and oedema. Anaphylactic shock or severe delayed reactions may also occur. Commonly reported adverse effects with allergen preparations given **sublingually** include oral oedema, pruritus, and paraesthesia, throat irritation, sneezing, rhinitis, nasal congestion, itching of the eyes and ears, and headache; systemic reactions may occur if the dosage regimen is not adhered to.

Severe reactions to allergen products normally occur within 30 minutes and should be treated promptly with intramuscular adrenaline injection 1 in 1000 (1 mg/mL). Full supportive measures should be implemented and treatment with antihistamines and corticosteroids may be required (for a discussion of the treatment of anaphylaxis and anaphylactic shock, see p. 1293.2). Further allergen immunotherapy should be stopped or continued at reduced dosage depending on the severity of the reaction and in accordance with the licensed product information.

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In 1986 the UK CSM reported[1] that hyposensitising vaccines have the potential to induce severe bronchospasm and anaphylaxis, and that these reactions had caused 26 deaths in the UK since 1957. The majority of patients had no reaction to previous hyposensitising injections. In 1989 the FDA reported that since 1980, the American Academy of Allergy and Immunology and the FDA had received 14 reports of death after allergen immunotherapy, and 4 deaths after skin testing for allergies.[2] The most common clinical factor in these patients was a history of asthma.

In view of these and other reports, recommendations have been made to minimise the risks of systemic reactions.[3-6] Allergen immunotherapy should only be used for seasonal allergic rhinoconjunctivitis not responding to anti-allergic drugs, and for severe hypersensitivity to Hymenoptera stings. In the UK[4] such treatment has usually been avoided in patients with asthma (although asthma is not an absolute contra-indication to Hymenoptera allergen immunotherapy), but elsewhere[3,5,6] asthmatic patients whose asthma is stable and not severe may be treated. Hyposensitising agents should be used only where facilities for full cardiopulmonary resuscitation are immediately available. The recommended length of time after injection that patients should be kept under medical observation varies from 30 minutes[3] to 1 hour.[4] If the patient develops even mild symptoms of a general reaction, observation should be extended until they are completely resolved. The observation period should also be extended for patients at high risk of reactions.

Of 12 samples of *Aspergillus* extract used for allergen immunotherapy, 4 were found to contain aflatoxin (p. 2432.2), one being highly mutagenic as determined by the Ames' test. The results suggested that careful screening of commercially available mould extracts was warranted.[7]

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Precautions

Patients should be observed for at least 30 to 60 minutes after administration of allergen products because of the risk of anaphylaxis (see also under Adverse Effects, above). Patients should avoid taking beta blockers since adrenaline may be ineffective if hypersensitivity reactions occur. Antiallergic medication taken concomitantly may mask the patient's reactivity.

Skin-prick testing should not be carried out in areas where there are skin lesions. Patients should be instructed not to rub or scratch the test site. Antiallergic medication should be stopped before allergen testing to prevent false negative reactions. Systemic or long-term topical use of potent corticosteroids may also mask skin reactivity.

Allergen immunotherapy should not be used in patients with serious immunological illness, cancer, disorders of amino acid metabolism, bleeding disorders, or hyperthyroidism. It should also be avoided during infections or febrile conditions, and administration of an allergen preparation delayed for 24 to 48 hours after recovery. Allergen immunotherapy should be avoided during pregnancy because of the risk to the fetus of any systemic reactions in the mother. Patients with asthma may be more susceptible to hypersensitivity reactions with allergen products and it is considered that allergen immunotherapy should be avoided or used with caution. Injection immunotherapy should be avoided in children under 6 years of age, and sublingual immunotherapy in children under 2 years. Sublingual immunotherapy is contra-indicated in patients with severe oral inflammatory conditions such as lichen planus with ulcerations, or severe mycosis. Sublingual immunotherapy should be stopped for 7 days in patients who have oral surgery, including dental extraction, and also in children shedding a deciduous tooth, to allow the wounds to heal.

Allergen immunotherapy should be avoided or used with caution in patients with cardiovascular or pulmonary insufficiency, or severe eczema. Rarely, patients may have drowsiness with allergen immunotherapy preparations and, if affected, should avoid driving or operating machinery.

Allergen immunotherapy injections should only be given where facilities for full cardiopulmonary resuscitation are immediately available. Injections for immunotherapy should be given subcutaneously and not intravenously or intramuscularly. Patients should avoid strenuous exercise for at least 12 hours after injection immunotherapy, or 1 hour before and after sublingual immunotherapy. It is also recommended to avoid heavy meals and alcohol around the time of injection with some products. Severe anaphylactoid reactions have been reported in patients undergoing allergen immunotherapy who are also receiving ACE inhibitors (see Hypersensitivity, p. 1287.1). Some manufacturers suggest that the reaction could be avoided by temporarily withholding ACE inhibitor therapy during each desensitisation. Allergen immunotherapy preparations and vaccines against infectious diseases should not be given within at least a week of each other or until all possible reactions to either vaccine have disappeared.

Interactions

For precautions to be observed in using allergen products in patients receiving ACE inhibitors, antiallergic drugs, beta blockers, corticosteroids, or vaccines see Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Albay†; Allpyral†; *Austria*: Grazax; Oralair; *Belg.*: Alyostal; Oralair; Pharmalgen; True Test†; *Braz.*: Nikkho Vac; *Canad.*: Oralair; Pharmalgen†; Pollinex-R; Venomil; *China*: Alutard SQ (安脱达); ChangDi (畅迪); Novo-Helisen (阿罗格); *Cz.*: Alutard SQ; Alyostal; D-Al; Grazax; H-AL; Oralair; Pangramin; Pollinex; Soluprick SQ; Staloral; *Denm.*: ALK; Alutard SQ; Aquagen SQ; Grazax; Nixema†; Pharmalgen; Soluprick; True Test; *Fin.*: Grazax; *Fr.*: Albay; Alyostal; ASAD†; Diallertest; Grazax; True Test; *Ger.*: Acaroil; ALK; Allergovit; Clustoid; Depiquick; Depot-Hal; Grazax; Hyminox†; Novo-Helisen; Oralair; Oralvac; Phostal; Pollinex Quattro; Purethal; Reless; Roxoid; Staloral; TA Baume; TA Graser; TA Krauter top; TA MIX†; Tol†; TyroMILBE; Tyrosin TU; Venomenhal; Venomil; *Gr.*: Alyostal; Grazax; Staloral; *Hung.*: Alyostal; Alyostal; Lais; Pangramin; Purethal; Staloral; Venomenhal; *Irl.*: Grazax; *Israel*: Ingestants Extracts; Inhalants And Epidermal Extracs; Insects Extracts; Mold & Smuts Extracts; True Test; *Ital.*: Grazax; Phostal†; Staloral†; *Neth.*: Allergopharma; Allergovit; Alutard; ARTU; Artuvac; Bencard Priktestoplossing; Depot-Hal; Grazax; HAL; Keolium; Nixema†; Novo-Helisen†; Oralair; Oralgen; Pharmalgen; Pollinex; Purethal; Soluprick Controlevloeistoffen; Soluprick SQ; *Norw.*: Alutard; Grazax; Soluprick SQ; *NZ*: Albey; True Test; *Pol.*: Allergovit; Alutard SQ; Alyostal; Catalet; Grazax; Novo-Helisen; Perosal; Pharmalgen; Phostal; Pollinex; Purethal; Staloral; Venomenhal; *Port.*: Grazax; Soluprick; Truetest; *Rus.*: Fostal (Фосталь); Ungapiven (Унгапивен); *S.Afr.*: Albay†; Albey†; Allpyral Pure Mite†; Allpyral Special Grass†; *Spain*: Grazax; Oralair; *Swed.*: Alutard SQ; Aquagen SQ; Grazax; Mekostest; Soluprick SQ; *Switz.*: ALK; Allergovit; Alutard SQ; Alyostal†; Grazax; Novo-Helisen; Oralair; Pharmalgen; Phostal; Polvac; Soluprick SQ; Staloral; *Turk.*: Acaril; Acarosan; Allergodip; Allergopen; Allergovit; Apsi; Novo-Helisen; *UK*: Bencard Skin Testing Solutions; Grazax; Pharmalgen; Pollinex; Soluprick SQ; *USA*: Albay†; Allpyral; Center-Al; Pharmalgen; True Test; Venomil†.

Multi-ingredient Preparations. *Arg.*: Summavac; *Braz.*: Alergonil; Aminovac; Urtivac; Vag Oral†; *Canad.*: Center-AL; True Test; *Cz.*: Phostal; *Fin.*: Alutard SQ; Aquagen SQ; Soluprick SQ; *Ger.*: Alustal; Avanz; BU Pangramin SLIT†; Depigoid; Depot Slit One; Sublivac; Sulgen; *Gr.*: Allergopharm; *Ital.*: Alustal†; *Neth.*: Trolab; True Test; *NZ*: Alustal; *Switz.*: Alustal; True Test.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex; Tonsillopas; *Ger.*: Schworosin; Tonsillopas; *Switz.*: Regenaplex Nr 28b; Regenaplex Nr 41a; Regenaplex Nr. 25b.

Allyl Isothiocyanate *(USAN)*

Аллилизотиоцианат.

Isothiocyanato-1-propene.

C_4H_5NS=99.15

CAS — 57-06-7.

UNII — BN34FX42G3.

Pharmacopoeias. *Fr.* and *US*

USP 36: (Allyl Isothiocyanate). A colourless to pale yellow, very refractive, liquid with a pungent, irritating odour and an acrid taste. Slightly soluble in water; miscible with

alcohol, with carbon disulfide, and with ether. Store in airtight containers.

Profile

Allyl isothiocyanate is the main constituent of volatile mustard oil (p. 2646.1) derived from black mustard seeds (p. 2566.1). It is an extremely powerful irritant that has been used as a counter-irritant and rubefacient.

Handling. Allyl isothiocyanate is a potent lachrymator, with a pungent irritating odour. Care should be taken to protect the eyes, to prevent inhalation of fumes, and to avoid tasting.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Apisarthron; *Ukr.*: Апісартрон (Апісартрон).

Almond Oil

Aceite de Almendra; Aceite de almendras; Almendras dulces; aceite de Amande; huile d'Amygdalae Oleum; Badem Yağı; Bitter Almond Oil; Expressed Almond Oil; Huile d'Amande; Mandelöl; Mandelolja; Mandlový olej; Mandulaolaj; Mantelioliy; Migdolų aliejus; Ol. Amygdal.; Olej migdałowy; Oleo de Amêndoas; Olio di Mandorla; Sweet Almond Oil; Миндальное Масло.

CAS — 8007-69-0.

ATC Herb — HD02WB5008 (Prunus dulcis oil).

UNII — 66YXD4DKO9 (almond oil); 6TQK77W0EX (bitter almond oil).

Pharmacopoeias. In *USNF*.

Eur (see p. vii) includes the virgin oil and a refined oil.

Pr. also specifies Huile de Noyaux, an oil obtained from various species of *Prunus*.

Ph. Eur. 8: (Almond Oil, Virgin; Amygdalae Oleum Virginale). A yellow, clear, liquid. It is the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* var. *amara* or *P. dulcis* var. *dulcis* or a mixture of both varieties. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 8: (Almond Oil, Refined; Amygdalae Oleum Raffinatum). The fatty oil obtained by refining and deodorisation of Almond Oil. It may contain a suitable antoxidant. A pale yellow, clear liquid. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

USNF 31: (Almond Oil). The refined fixed oil expressed from the kernels of varieties of *Prunus dulcis*[*Prunus amygdalus*] (Rosaceae). It may contain suitable antoxidants. A clear, colourless or pale straw-coloured, oily liquid with a bland taste. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in well-filled, airtight containers. Protect from light.

Profile

Almond oil, which consists mainly of glycerides of oleic acid with smaller amounts of linoleic and palmitic acid, has nutritive and demulcent properties. It is used as an emollient and to soften ear wax. It is also used as a vehicle in some injections.

Reviews.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Laderm; *Gr.*: Karelyne.

Multi-ingredient Preparations. *Arg.*: Calen†; *Austral.*: Curash Babycare Medicated Nappy Rash Cream; *Canad.*: Pure Gardens; *Chile*: Akerat; *Cz.*: Balmandol; *Fr.*: Aromadetox†; *Ger.*: Neuroderm; *Irl.*: Barex†; *Ital.*: Activ Dopo Puntura†; Baby Zanzara†; Babygella; Babysteril; *Mex.*: Liniderm; *NZ*: Am-O-Lin†; Snorenz; *Port.*: Cuidaderma; Olidermil; *Singapore*: Earex; Snoreeze; *Spain*: Pasta Lassar Imba; *Switz.*: Antidry; Antidry; Antidry; Balmandol; Viola; *Turk.*: Balmandol; Metamorfoz; Myo-Oil; Snoreless; *UK*: Calendula Nappy Change Cream; Earex; Imuderm†; Infaderm; Skin Perfecting Oil; Snor-Away.

Pharmacopoeial Preparations

BP 2014: Almond Oil Ear Drops;

USP 36: Rose Water Ointment.

Alpha Fetoprotein

ABI-001 (recombinant AFP); α-Fetoprotein; MM-093 (recombinant AFP).

Profile

Alpha fetoprotein (AFP) is a naturally occurring alpha globulin of similar molecular weight to albumin. It is the most abundant plasma protein found in the human fetus and screening of AFP concentrations in maternal serum and amniotic fluid may be used for the detection of developmental abnormalities. Elevated concentrations of alpha fetoprotein are used as a marker test for various cancers and as a way of monitoring treatment in hereditary tyrosinaemia type 1 (see p. 2572.2).

Recombinant alpha fetoprotein has been investigated in the treatment of auto-immune diseases, but concerns about a potential oncogenic effect have been raised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Profetal (Профеталь).

Alpha Galactosidase A

α-D-Galactosidase; α-Galactosidase A; α-D-Galactoside Galactohydrolase; Альфа-галактозидаза А.

UNII — 6215K8E2M8 (Aspergillus niger alpha-galactosidase).

Agalsidase Alfa *(BAN, USAN, rINN)*

Agalsidasa alfa; Agalsidasum Alfa; Агальсидаза Альфа.

CAS — 104138-64-9 (protein moiety).

ATC — A16AB03.

ATC Vet — QA16AB03.

UNII — 2HLC17MX9G.

Agalsidase Beta *(rINN)*

Agalsidasa β; Agalsidasum Beta; Agalsidaz Beta; Alfasidasa β; Агальсидаза Бета.

CAS — 104138-64-9 (protein moiety).

ATC — A16AB04.

ATC Vet — QA16AB04.

UNII — RZD65TSM9U.

Uses and Administration

Alpha galactosidase A is an endogenous enzyme that hydrolyses terminal α-D-galactose residues in oligosaccharides and galactolipids into more easily digestible mono- and disaccharides. A form derived from a fungal source is used to prevent intestinal gas.

Agalsidase alfa and beta are recombinant forms of alpha galactosidase A used for the long-term enzyme replacement therapy of Fabry disease (see below).

Agalsidase alfa is given by intravenous infusion in a dose of 200 micrograms/kg over 40 minutes, repeated every alternate week.

Agalsidase beta is given by intravenous infusion in a dose of 1 mg/kg at an initial rate of no more than 250 micrograms/minute; once tolerance has been established, for patients weighing ≥30 kg, the rate of administration may be gradually increased by 50 to 80 micrograms/minute in each subsequent infusion. The dose should be repeated every alternate week.

Administration in children. Licensed product information suggests that agalsidase alfa may be given to children aged 7 years and older, and agalsidase beta to children 8 years and over, for the treatment of Fabry disease in the doses outlined above.

Fabry disease. Fabry disease (Anderson-Fabry disease) is a rare X-linked recessive lysosomal storage disorder. It mainly affects males, although female carriers may sometimes have clinical manifestations. It is characterised by a deficiency of the enzyme alpha galactosidase A resulting in the intracellular accumulation of globotriaosylceramide (Gb_3) and other glycosphingolipids, especially in vascular endothelium and smooth muscle. Symptoms include severe neuropathies, fevers, skin blemishes (angiokeratomas), corneal and lenticular opacities, and gastrointestinal disturbances. Cardiac, cerebrovascular, and renal deterioration is progressive placing patients at increased risk for early-onset myocardial infarction, stroke, and renal failure.[1-7]

Symptomatic treatment was the only option until the development of enzyme replacement therapy[3,6] with agalsidase alfa[2,8] and beta.[7,9] Results from controlled studies show this form of therapy to be effective in clearing deposits from the kidneys, heart, and skin[10-14] as well as improving peripheral neuropathy.[15] An open-label extension study[16] of agalsidase beta in the 58 patients formerly studied in a 20-week controlled phase III study[12] confirmed the continued safety and efficacy of enzyme replacement therapy after 30 months of treatment. Benefit continued in these patients followed up for a further 24 months,[17] and kidney biopsies in 8 of the patients confirmed complete clearance of globotriaosylceramide. A systematic review[4] of prospective randomised controlled and open-label studies concluded that the evidence for enzyme replacement therapy with agalsidase beta at a dose of 1 mg/kg every other week was more robust than that for agalsidase alfa at a dose of 200 micrograms/kg every other week, although the benefit with either dose or drug was variable. The cardiac effects of Fabry disease have been reviewed,[18] and both agalsidase alfa and beta have been reported to improve left ventricular structure and function. Further studies[19-21] confirmed regression of left ventricular hypertrophy with agalsidase alfa or beta, but improvement in myocardial function or exercise capacity is more likely to occur in patients started on enzyme replacement therapy before myocardial fibrosis is evident.[21] Although most studies have been in adults, enzyme replacement therapy has been shown to be safe in children over 6 years of age.[22] Expert opinion generally recommends that treatment is begun as soon as clinical signs and symptoms are seen.[4,23] Gene therapy[24] is also under investigation.

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4. Desnick RJ, *et al.* Fabry disease in childhood. *J Pediatr* 2004; 144: 520–526.
5. Clarke JTR. Narrative review: Fabry disease. *Ann Intern Med* 2007; 146: 425–33.
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9. Keating GM, Simpson D. Agalsidase beta: a review of its use in the management of Fabry disease. *Drugs* 2007; 67: 435–55.
10. Moore DF, *et al.* Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001; 104: 1506–12.
11. Schiffmann R, *et al.* Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001; 285: 2743–9.
12. Eng CM, *et al.* Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001; 345: 9–16.
13. Moore DF, *et al.* Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002; 33: 525–31.
14. Wraith JE, *et al.* Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *J Pediatr* 2008; 152: 563–70.
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16. Wilcox WR, *et al.* Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet* 2004; 75: 65–74.
17. Germain DP, *et al.* Sustained, long-term renal stabilization after 54 months of agalsidase β therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007; 18: 1547–57.
18. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart* 2007; 93: 528–35.
19. Hughes DA, *et al.* Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008; 94: 153–8.
20. Imbriaco M, *et al.* Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: a prospective long-term cardiac magnetic resonance imaging study. *Heart* 2009; 95: 1103–7.
21. Weidemann F, *et al.* Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation* 2009; 119: 524–9.
22. Ries M, *et al.* Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006; 118: 924–32.
23. Banikazemi M, *et al.* Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007; 146: 77–86.
24. Stanicka C, Medin JA. Gene therapy for Fabry disease. *J Inherit Metab Dis* 2001; 24 (suppl 2): 25–41.

Adverse Effects, Treatment, and Precautions

Infusion reactions have been reported in about 14% of patients given agalsidase alfa, and in about 67% of patients treated with agalsidase beta. The frequency of onset of these reactions decreases with continued use, with the majority of reports occurring during the first 2-4 months after the start of treatment, although onset after 1 year has also been reported. Symptoms generally start during, or within 1 hour of, infusion. The most common symptoms have included chills, dyspnoea, facial flushing, headache, nausea, fever, and fatigue. Other reported symptoms include abdominal pain, diarrhoea, vomiting, nasal congestion, throat tightness, chest pain, dizziness, paraesthesia, myalgia, stridor, hypoxia, hypertension, bradycardia, tachycardia, and pruritus, urticaria, and angioedema; anaphylactic shock has also been noted rarely. The infusion may be interrupted for about 5 to 10 minutes and restarted once symptoms have subsided. Pre-treatment with oral antihistamines, paracetamol, ibuprofen, and/or corticosteroids 1 to 24 hours before infusion has been used to prevent subsequent reactions. Patients with compromised cardiac function due to Fabry disease should be monitored closely since they may be predisposed to a higher risk of severe complications arising

from infusion reactions. IgG antibodies to agalsidase alfa develop in some patients, and to agalsidase beta in the majority of patients. The presence of antibodies increases the risk of infusion reactions. Serious hypersensitivity reactions including anaphylactic shock have been reported during infusion with agalsidase alfa or beta.

Interactions

Agalsidase alfa or beta should not be used with amiodarone, chloroquine, monobenzone, or gentamicin, which all have the potential to inhibit intracellular α-galactosidase activity.

Pharmacokinetics

The pharmacokinetic properties of agalsidase alfa appear to be unaffected by dose; the elimination half-life from blood after a single dose has been reported to be about 100 minutes. The pharmacokinetics of agalsidase beta indicate a saturated clearance; the elimination half-life after a single dose has been reported to range from 45 to 100 minutes.

Most pharmacokinetic parameters of agalsidase alfa in children with Fabry disease were similar to those in adult patients after single and repeated doses, except for serum clearance, which was age dependent being significantly increased in children.[1] However, there was no difference in pharmacodynamics between the age groups.

1. Ries M, *et al.* Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J Clin Pharmacol* 2007; 47: 1222–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Fabrazyme; Replagal; *Austria*: Fabrazyme; Replagal; *Belg.*: Fabrazyme; Replagal; *Braz.*: Fabrazyme; *Canad.*: Beano; Fabrazyme; Gaz Away†; Replagal; *Chile*: Fabrazyme; *Cz.*: Fabrazyme; Replagal; *Denm.*: Fabrazyme; Replagal; *Fin.*: Fabrazyme; *Fr.*: Fabrazyme; Replagal; *Ger.*: Fabrazyme; Replagal; *Gr.*: Fabrazyme; Replagal; *Hong Kong*: Fabrazyme; *Hung.*: Fabrazyme; Replagal; *India*: Galazyme-A; Galazyme-Pro; Leno; *Irl.*: Fabrazyme; Replagal; *Israel*: Fabrazyme; Replagal; *Ital.*: Fabrazyme; Replagal; *Jpn*: Fabrazyme; *Malaysia*: Fabrazyme; *Neth.*: Fabrazyme; Replagal; *Norw.*: Fabrazyme; Replagal; *NZ*: Fabrazyme; Replagal; *Pol.*: Fabrazyme; Replagal; *Port.*: Fabrazyme; Replagal; *Rus.*: Fabrazyme (Фабразим); Replagal (Реплаган); *Spain*: Fabrazyme; Replagal; *Swed.*: Fabrazyme; Replagal; *Switz.*: Fabrazyme; Replagal; *Turk.*: Fabrazyme; *UK*: Beano; Fabrazyme; Replagal; *USA*: Beano; Fabrazyme.

Multi-ingredient Preparations. *India*: Blotamax; Gastica Plus; Leno-EZ; *Ital.*: No Gas Enzimi.

Alpha$_1$-proteinase Inhibitor

alpha-1-Antitrypsinum; Alpha$_1$ Antitrypsin; Antitrypsine alpha-1; Inhibidor de la α_1-proteinasa; Альфа1 Антитрипсин.

ATC — B02AB02.

ATC Vet — QB02AB02.

UNII — F43I396OJS (alpha$_1$-proteinase inhibitor human).

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

Ph. Eur. 8: (Human α-1-Proteinase Inhibitor). A sterile liquid or freeze-dried preparation of a plasma protein fraction containing mainly human α-1-proteinase inhibitor. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Other plasma proteins may be present. It may contain excipients such as stabilisers. Freeze-dried products are hygroscopic, white or pale yellow or pale brown powders or friable solids; liquid products are clear or slightly opalescent, colourless or pale yellow or pale green or pale brown. pH of 6.5 to 7.8. Store in airtight and sterile containers at a temperature not exceeding 25 degrees.

Uses and Administration

Endogenous alpha$_1$-proteinase inhibitor is a serum glycoprotein synthesised in the liver that acts as an elastase inhibitor, mainly inhibiting neutrophil elastase. Alpha$_1$-proteinase inhibitor, prepared from pooled human plasma, is used as replacement therapy in patients with emphysema who have congenital alpha$_1$ antitrypsin deficiency (see below). It is given in a dose of 60 mg/kg once a week by intravenous infusion at a rate of about 0.08 mL/kg per minute (usually corresponding to a 15 to 30 minute infusion).

A recombinant form of alpha$_1$-proteinase inhibitor is under investigation for nebulised delivery in congenital alpha$_1$ antitrypsin deficiency and cystic fibrosis (see below).

Alpha$_1$-proteinase inhibitor has also been investigated for the prevention of bronchopulmonary dysplasia (p. 1602.1) in preterm neonates.

Alpha$_1$ antitrypsin deficiency. Alpha$_1$ antitrypsin deficiency (alpha$_1$-proteinase inhibitor deficiency) is characterised by chronic obstructive pulmonary disease (COPD) and chronic liver disease associated with a lack of alpha$_1$-proteinase inhibitor.[1,2] This inhibitor is produced in the liver but exerts its main effects in the lungs as an inhibitor of neutrophil elastase, an enzyme released in response to inflammation. Congenital deficiency of the inhibitor thus leaves the lungs vulnerable to destruction by elastase, leading to the development of emphysema (see Chronic Obstructive Pulmonary Disease, p. 1199.1), usually in the third or fourth decade of life. Hepatic manifestations of deficiency include hepatitis, cirrhosis, and hepatoma. Panniculitis and vasculitis may also occur less frequently in some phenotypes.[3,4]

Management of COPD associated with the deficiency involves avoidance of factors (mainly cigarette smoking) that cause pulmonary inflammation, and supportive treatment with bronchodilators and oxygen as appropriate. Augmentation therapy with alpha$_1$-proteinase inhibitor to raise serum concentrations above the protective threshold is also of benefit in some patients.[3,5] Intravenous infusion of the drug has been shown to correct the biochemical abnormality[6] and has been recommended in those patients with some deterioration of lung function.[3,7] In a short-term study[8] serum and secretion concentrations of alpha$_1$-proteinase inhibitor as well as markers of neutrophilic inflammation were monitored in 12 patients receiving augmentation therapy over 4 weeks. Results showed a rise in serum levels of alpha$_1$-proteinase inhibitor to above the protective threshold, and reduction in elastase activity and levels of leukotriene B_4 levels (thought to be important in producing airway inflammation in alpha$_1$ antitrypsin deficiency). A small placebo-controlled study[9] found that the rate of decline of FEV_1 was not affected in patients treated for at least 3 years. Data[10] from a large registry of patients also suggested that, overall, treatment did not affect the rate of decline of FEV_1, but that it decreased mortality, although this may be influenced by other factors. Evaluation[7] of 2 of these studies[9,10] and one other concluded that replacement therapy might reduce the progression of disease in selected patients, but that further randomised placebo-controlled studies were required to provide conclusive evidence for overall clinical efficacy. The Canadian Thoracic Society[11] recommends that replacement therapy should be reserved for patients with an FEV_1 between 35 and 65% predicted who are no longer smoking and on optimal medical therapy but continuing to show a rapid decline in FEV_1. In a retrospective cohort study[12] in 96 patients followed up for a minimum of 12 months, results indicated that the rate of progression of pulmonary emphysema was reduced during the time that the patients received augmentation therapy, and patients with well-maintained lung function and a rapid decline in FEV_1 benefited most from therapy. These authors recommended early diagnosis to identify patients at risk and to start augmentation even if lung function is greater than 65% predicted.

Liver involvement does not respond to treatment with alpha$_1$-proteinase inhibitor and is managed symptomatically.[3]

Several new approaches to treatment of alpha$_1$ antitrypsin deficiency are under investigation:[3,4,13] plasma-derived and recombinant forms of alpha$_1$-proteinase inhibitor for inhalation; synthetic elastase inhibitors for oral use; synthetic chaperones to block intrahepatic polymerisation of the inhibitor and other methods to improve serum concentrations; retinoids; inhaled hyaluronic acid; and gene therapy.

1. Köhnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. *Am J Med* 2008; 121: 3–9.
2. Silverman EK, Sandhaus RA. Alpha$_1$-antitrypsin deficiency. *N Engl J Med* 2009; 360: 2749–57.
3. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; 168: 818–900. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/alpha1.html (accessed 14/07/06)
4. Stoller JK, Aboussouan LS. α$_1$-Antitrypsin deficiency. *Lancet* 2005; 365: 2225–36.
5. Juvelekian GS, Stoller JK. Augmentation therapy for α$_1$-antitrypsin deficiency. *Drugs* 2004; 64: 1743–56.
6. Coakley RJ, *et al.* α1-Antitrypsin deficiency: biological answers to clinical questions. *Am J Med Sci* 2001; 321: 33–41.
7. Abboud RT, *et al.* Alpha$_1$-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J* 2001; 8: 81–8.
8. Stockley RA, *et al.* The effect of augmentation therapy on bronchial inflammation in α 1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2002; 165: 1494–8.
9. Dirksen A, *et al.* A randomized clinical trial of α$_1$-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; 160: 1468–72.
10. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of α$_1$-antitrypsin. *Am J Respir Crit Care Med* 1998; 158: 49–59.
11. O'Donnell DE, *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J* 2007; 14 (suppl B): 5B–32B.
12. Wencker M, *et al.* Longitudinal follow-up of patients with α$_1$-protease inhibitor deficiency before and during therapy with IV α$_1$-protease inhibitor. *Chest* 2001; 119: 737–44.
13. Sandhaus RA. α$_1$-Antitrypsin deficiency 6: new and emerging treatments for α$_1$-antitrypsin deficiency. *Thorax* 2004; 59: 904–9.

Cystic fibrosis. Some of the inflammatory damage that occurs in the lungs of patients with cystic fibrosis is thought to be caused by excessive amounts of elastase released locally. Alpha$_1$-proteinase inhibitor given by nebuliser is therefore under investigation[1-3] in patients with cystic fibrosis (p. 177.2).

1. Martin SL, *et al.* Safety and efficacy of recombinant alpha$_1$-antitrypsin therapy in cystic fibrosis. *Pediatr Pulmonol* 2006; 41: 177–83.
2. Cantin AM, *et al.* Prolastin aerosol therapy and sputum taurine in cystic fibrosis. *Clin Invest Med* 2006; 29: 201–7.
3. Griese M, *et al.* α$_1$-Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *Eur Respir J* 2007; 29: 240–50.

Adverse Effects and Precautions

Adverse effects of intravenous alpha$_1$-proteinase inhibitor include asthenia, chills, increase in cough, dizziness, dyspnoea, flu-like symptoms, headache, hypotension, pain at the injection site, paraesthesias, pharyngitis, pruritus, rashes, somnolence, and tachycardia. The infusion should be interrupted or the rate reduced if adverse effects occur and resumed at a more tolerable rate once the symptoms have subsided; the infusion should be stopped immediately in the event of anaphylactic or anaphylactoid reactions, and full supportive measures implemented. Preparations derived from pooled human plasma carry a risk of transmission of infection (see Blood, p. 1135.3).

The drug is contra-indicated in patients with selective IgA deficiencies who have known antibody against IgA since they are at risk of severe reactions to IgA that may be present in the product.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aralast; Prolastin; Trypsan; *Austria*: Prolastin; *Canad.*: Prolastin; *Chile*: Trypsan; *Cz.*: Trypsone; *Denm.*: Prolastina; *Fin.*: Prolastina; *Fr.*: Alfalastin; *Ger.*: Prolastin; *Gr.*: Aralast; Prolastin; *Irl.*: Prolastin; *Israel*: Glassia; *Ital.*: Prolastina; *Neth.*: Prolastin; *Port.*: Prolastin; *Spain*: Prolastina; Trypsone; *Swed.*: Prolastina; *Switz.*: Prolastin; *USA*: Aralast; Prolastin; Zemaira.

Althaea

Altea; Alteablad (marshmallow leaf); Altearot (marshmallow root); Alteeanjuuri (marshmallow root); Alteeanlehti (marshmallow leaf); Alteia; Alth.; Althaca; Althaea folium (marshmallow leaf); Althaeae radix (marshmallow root); Bismalva; Eibisch; Guimauve; Guimauve, feuille de (marshmallow leaf); Guimauve, racine de (marshmallow root); Hierba cañamera; Korzeń prawoślazu (marshmallow root); Liść prawoślazu (marshmallow leaf); Malvavisco; Marshmallow; Orvosiziliz-gyökér (marshmallow root); Orvosiziliz-levél (marshmallow leaf); Proskurníkový kořen (marshmallow root); Proskurníkový list (marshmallow leaf); Svilarožių lapai (marshmallow leaf); Svilarožių šaknys (marshmallow root); Алтеи.

ATC — R05CA05.

ATC Vet — QR05CA05.

ATC Herb — HD02WA5002 (Althaea officinalis: root); HA01WB5001 (Althaea officinalis: root; HR05DB5002 (Althaea officinalis: root).

UNII — TRW2FUF47H (Althaea officinalis root).

Pharmacopoeias. *Eur.* (see p. vii) includes the root and the leaf. *Fr.* also includes the flower.

Ph. Eur. 8: (Marshmallow Root; Althaeae Radix). The peeled or unpeeled, whole or cut, dried root of marshmallow, *Althaea officinalis*. Protect from light.

Ph. Eur. 8: (Marshmallow Leaf; Althaea Folium). The whole or cut dried leaf of *Althaea officinalis*. Protect from light.

Profile

Althaea is demulcent and emollient and has been used for irritation and inflammation of the mucous membranes of the mouth and pharynx, and relief of associated dry cough. It has also been used in traditional remedies for a variety of disorders including gastrointestinal disturbances.

General references.

1. WHO. Radix Altheae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/3.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Colluvoxyl†; Primadrill†; *Ger.*: Phytohustil; *Pol.*: Althagem; Althamel; Rubital; *Ukr.*: Alteyka (Алтейка); Althemix (Алтемікс)†; Mucaltin Forte (Мукалтин Форте).

Multi-ingredient Preparations. *Arg.*: Pansoral Primeros Dientes; *Austral.*: Althaea Complex†; Digestive Aid; Garlic and Horseradish + C Complex†; Herbal Throat Spray; Ultra Allergy Defense; *Austria*: Heumann's Bronchialtee; Hustensaft Weleda; The Chambard-Tee; Tuscalman; *Belg.*: Sedemol; Sulfa-Sedemol; *Canad.*: Bilonat; Honey Herb Cough Drops†; Original Herb Cough Drops†; *Cz.*: Detska Cajova Smes; Detsky Caj s Hermankem; Pruduskova; Pulmoran; Species Pectorales Planta; *Fr.*: Apilaxe; Boribel Tisane No 13†; Boribel Tisane No 6†; Colitisane†; Pansoral Premieres Dents; Pectoflorine†; Tisane D'Ars†; Tisane Provencale no 1; Tisane Saint-Urbain†; *Ger.*: Heumann Bronchialtee Solubifix T; Imupret; Weleda Hustenelixier; *Hung.*: Majvedo es Detoxikalo; *Indon.*: Silex; *Ital.*: Altuss; Bron 6; Enatus; Gastrotuss; *Neth.*: Verzachtende Hoestsiroop met tijm; *Pol.*: Bronchial†; Gastrosan fix†; Rubital Compositum; Syrop Prawoslazowy Zlozony; Tabulettae Laxantes; *Rus.*: Linkus (Линкас); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Pansoral Teething (Пансорал Первые Зубы); Pectorales Species No 1 (Грудной Сбор 1); Pectorales Species No 3 (Грудной Сбор 3); Tonsilgon N (Тонзилгон Н); *S.Afr.*: Cough Elixir†; *Singapore*: Pansoral Teething†; *Switz.*: Elixir contre la toux†; Malveol; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; Tisane Provencale no 1; Tuscalman; *UK*: Herb and Honey Cough Elixir; Herbheal Ointment; Modern Herbals Cold & Catarrh; Potter's Catarrh Pastilles; Sinotar; *Ukr.*: Bronchostop (Бронхостоп); Imupret (Імупрет); Linkus (Линкас); Mucaltin Forte с Vitamini C (Мукалтин Форте с витамином С); Tonsilgon N (Тонзилгон)†; *Venez.*: Novacodin.

Homoeopathic Preparations. *Fr.*: Poconeol no 37; *UK*: Cough Elixir.

Alum

Alaun; Allume; Aluin; Alumbre; Alumen; Aluminium Kalium Sulfuricum; Aluminium Potassium Sulfate; Aluminium Potassium Sulphate; Aluminiumkaliumsulfat; Aluminium-kálium-szulfát; Aluminum Potassium Sulfate; Alun; Aluna; Alūnas; E522; Glinowo-potasowy siarczan; Glinu potasu siarczan; Kalii Aluminii Sulfas Dodecahydricus; Potash Alum; Potassium Alum; Síran draselno-hlinitý dodekahydrát; Sulfato aluminico potásico; Sulfato de aluminio potasio; Квасцы; Алюм.

Potassium aluminium sulphate dodecahydrate.

$AlK(SO_4)_2.12H_2O$=474.4

CAS — 7784-24-9 (alum dodecahydrate); 10043-67-1 (anhydrous alum).

ATC — S01XA07.

ATC Vet — QS01XA07.

UNII — 1L24V9R23S (alum); 09OXB01F3O (anhydrous alum).

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

US also includes dodecahydrated ammonia alum (Ammonium Alum). *Jpn* also includes dried alum.

Ph. Eur. 8: (Alum). Colourless, transparent, crystalline masses or a granular powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. A 10% solution in water has a pH of 3.0 to 3.5.

USP 36: (Potassium Alum). A white powder or large, colourless crystals or crystalline fragments. It is odourless. Soluble 1 in 7 of water and 1 in 0.3 of boiling water; insoluble in alcohol; freely but slowly soluble in glycerol. Its solutions are acid to litmus. Store in airtight containers.

Uses and Administration

Alum precipitates proteins and is a powerful astringent. It is often included in preparations used as mouthwashes or gargles and in dermatological preparations.

Alum, either as a solid or as a solution, may be used as a haemostatic. Intravesical instillation of alum, typically as a 1% solution, has been used as a treatment for haemorrhagic cystitis (p. 2347.3).

Alum has been used as an adjuvant in the preparation of vaccines. It is also used as a mordant in the dyeing industry.

Adverse Effects and Precautions

Large doses of alum are irritant and may be corrosive; gum necrosis and gastrointestinal haemorrhage have occurred. Systemic absorption from bladder irrigation solutions can cause acute aluminium toxicity (see under Aluminium below) including encephalopathy.

Acute encephalopathy has been reported[1,2] after bladder irrigation with alum solutions in the treatment of bladder haemorrhage. Anecdotal evidence would suggest that this practice should be avoided in patients with renal insufficiency.[1]

1. Phelps KR, *et al.* Encephalopathy after bladder irrigation with alum: case report and literature review. *Am J Med Sci* 1999; 318: 181–5.
2. Nakamura H, *et al.* Acute encephalopathy due to aluminium toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; 40: 296–300.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Stepton; Varikopax.

Multi-ingredient Preparations. *Arg.*: Bentophyto; *Austria*: EST; *Braz.*: Lucretin; *Canad.*: Fletchers Sore Mouth Medicine; *Fr.*: Supro; *Ger.*: Retterspitz Ausserlich; Retterspitz Innerlich; *India*: Feel Chill†; *Irl.*: Pedamed; *Ital.*: Lavanda Sofar; *Mex.*: Porcremol; *Neth.*: Trachitol; *NZ*: Grans Remedy; *Spain*: Co Bucal; Lindemil; *USA*: BFI; Massengill; Mycinette; *Venez.*: Borogin.

Homoeopathic Preparations. *Fr.*: Poconeol no 82†; Sulfur Complexe No 12.

Aluminium

Aluminio; Aluminum; E173; Glin; Алюминий.

Al=26.9815386.

CAS — 7429-90-5.

UNII — CPD4NFA903 (aluminium); 3XHB1D032B (aluminium ion).

Description. Aluminium is a malleable and ductile soft silvery-white metal, becoming coated with a thin layer of oxide.

Pharmacopoeias. *Br.* includes Aluminium Powder.

BP 2014: (Aluminium Powder). An odourless or almost odourless, silvery-grey powder. It consists mainly of metallic aluminium in very small flakes, usually with an appreciable quantity of aluminium oxide. It is lubricated with stearic acid to protect the metal from oxidation. Practically insoluble in water and in alcohol; it dissolves in dilute acids and in aqueous solutions of alkali hydroxides, with the evolution of hydrogen.

Handling. Aluminium powder has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Incompatibility. Incompatibilities have been reported between aluminium in injection equipment and metronidazole,[1,2] and between aluminium and various antineoplastics including cisplatin, daunorubicin, and doxorubicin.[3-6] The suitability of aluminium caps for sugar-containing liquids has also been questioned. Abrasion of the aluminium cap by sugar from *Ceporex Syrup*[cefalexin] has resulted in the formation of a black slime.[7]

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; 42: 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; 42: 2660.
3. Bohart RD, Ogawa G. An observation on the stability of cis-dichlorodiamminepladnum (II): a caution regarding its administration. *Cancer Treat Rep* 1979; 63: 2117–18.
4. Gardiner WA. Possible incompatibility of doxorubicin hydrochloride with aluminum. *Am J Hosp Pharm* 1981; 38: 1276.
5. Williamson MJ, *et al.* Doxorubicin hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1983; 40: 214.
6. Ogawa GS, *et al.* Dispensing-pin problems. *Am J Hosp Pharm* 1985; 42: 1042.
7. Tressler LJ. Medicine bottle caps. *Pharm J* 1985; 235: 99.

Uses and Administration

Aluminium is used in packaging and in injection equipment. The foil is also used as a dressing and for insulation. Aluminium may also be employed as a colouring agent for some foodstuffs. Aluminium powder alone and in paste form with zinc oxide has been used as a dressing. Astringent aluminium salts are used as antiperspirants. Aluminium hydroxide (p. 1817.2) is used as an antacid.

Aluminium oxide (p. 1690.3) has been used as an abrasive agent.

Homoeopathy

Aluminium has been used in homoeopathic medicines under the following names: Aluminium metallicum; Alumin met; Al. met.

Adverse Effects, Treatment, and Precautions

Aluminium toxicity is well recognised in patients with renal impairment. Patients on dialysis have developed encephalopathy, osteodystrophy, and anaemia associated with an aluminium salt taken as a phosphate binder or with aluminium present in the water supply. For this reason, aluminium-free phosphate binders are often used in dialysis patients and the concentration of aluminium in dialysis fluid has been limited to not more than 10 micrograms/litre (see Aluminium Overload under Dialysis Solutions, p. 1779.3). Serum-aluminium concentrations should be monitored regularly in patients undergoing dialysis.

Aluminium toxicity has followed the use of parenteral fluids and infant feeds with a high concentration of aluminium.

Aluminium toxicity may be treated by removal of the aluminium with desferrioxamine (p. 1544.1).

The adverse effects of aluminium salts and precautions to be taken are described under Aluminium Hydroxide, p. 1817.3.

A review of aluminium toxicity[1] lists possible sources of aluminium including water, antacids, phosphate-binding gels, total parenteral nutrition solutions, processed human serum albumin, fluids used in infants, and environmental pollution; cooking utensils and beverages such as tea have also been suggested as possible sources of aluminium. It has been suggested that over-the-counter preparations of antacids, which can contain significant amounts of aluminium, represent the most important quantitative source of aluminium exposure.[2] Toxicity tends to occur when the gastrointestinal barrier to aluminium absorption is circumvented, as in intravenous fluid use or dialysis, or if the excretion of aluminium is reduced, as in renal impairment. Infants, especially preterm infants, form a special risk group.[3-7]

Accidental deposition of 20 tonnes of aluminium sulfate in a reservoir in Cornwall, UK in 1988 led to contamination of a nearby town's water supply.[8] Symptoms reported included diarrhoea, mouth ulcers or blisters, malaise, joint symptoms (mainly deterioration of existing symptoms), and memory defects (usually beginning 2 to 3 months after the incident). Although some medical experts considered that no long-term toxic effects were to be expected,[8] aluminium deposits were found in the bones of 2 individuals 6 to 7 months later.[9] In a study[10] undertaken 3 years after the incident, 55 adults who claimed to have suffered cerebral damage performed poorly in psychomotor testing. The authors attributed this to aluminium exposure, but the study's design and conclusions have been criticised.[11-13] An inquiry by the UK DoH[14] did not anticipate that exposure to aluminium from this incident would have caused long-term health problems in people who were adults or toddlers at the time, although this possibility should be explored further in those who were bottle-fed infants (i.e. below one year of age) at that time. Further studies were also recommended on the neuropsychological status and prevalence of joint problems in the population who consumed the contaminated water.

1. Monteagudo FSE, *et al.* Recent developments in aluminium toxicology. *Med Toxicol* 1989; 4: 1–16.
2. Reinke CM, *et al.* Aluminium in over-the-counter drugs: risks outweigh benefits? *Drug Safety* 2003; 26: 1011–25.
3. Bishop N, *et al.* Aluminium in infant formulas. *Lancet* 1989; i: 490.
4. Lawson M, *et al.* Aluminium and infant formulae. *Lancet* 1989; i: 614–15.
5. Anonymous. Aluminium content of parenteral drug products. *WHO Drug Inf* 1990; 4: 70.
6. American Academy of Pediatrics Committee on Nutrition. Aluminum toxicity in infants and children. *Pediatrics* 1996; 97: 413–16.
7. Pewtrell MS, *et al.* Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. *Pediatrics* 2009; 124: 1372–9. Correction. *Ibid.*: 1709.
8. Anonymous. Camelford two years on. *Lancet* 1990; 334: 366.
9. Eastwood JB, *et al.* Aluminium deposition in bone after contamination of drinking water supply. *Lancet* 1990; 334: 462–4.
10. Altmann P, *et al.* Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 1999; 319: 807–11.
11. David A. Cerebral dysfunction after water pollution incident in Camelford: results were biased by self selection of cases. *BMJ* 2000; 320: 1337.
12. Esmonde TFG. Cerebral dysfunction after water pollution incident in Camelford: study has several methodological errors. *BMJ* 2000; 320: 1337–8.
13. McMillan TM. Cerebral dysfunction after water pollution incident in Camelford: study may prolong the agony. *BMJ* 2000; 320: 1338.
14. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Subgroup Report on the Lowermoor Water Pollution Incident. DoH (issued 26th January, 2005). Available at: http://cot.food.gov.uk/pdfs/lowermoorreport05.pdf (accessed 16/08/10)

Burns. Thermal burns have been reported in patients undergoing magnetic resonance imaging (MRI) procedures when wearing transdermal medication patches containing aluminium in the backing material.[1] Aluminium is a conductive material and could induce a concentration of electrical currents sufficient to cause serious burns if placed in the MRI field; a similar phenomenon could also occur with external defibrillation.

1. Health Canada. Association of transdermal drug patches with thermal burns during magnetic resonance imaging procedures (issued 26th April 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/mri-irm_patch-timbre_nth-ah_e.pdf (accessed 03/04/08)

Effects on mental function. Encephalopathy with seizures has been associated with the use of aluminium-containing materials used for bone reconstruction.[1,2] In each case, reconstruction of areas of the skull resulted in high concentrations of aluminium in the CSF.

1. Renard JL, *et al.* Post-otoneurosurgery aluminium encephalopathy. *Lancet* 1994; 344: 63–4.
2. Hanson P, *et al.* Encephalopathy with seizures after use of aluminium-containing bone cement. *Lancet* 1994; 344: 1647.

ALZHEIMER'S DISEASE. The role of aluminium in the aetiology of Alzheimer's disease (see Dementia, p. 388.1) is, at best, unclear.[1-4] Circumstantial evidence of a positive association arises from *animal* and *in-vitro* data, together with clinical observations that aluminium is present in senile plaques and neurofibrillary tangles occurring in Alzheimer's disease, that giving aluminium chelators to Alzheimer patients may slow the progression of the disease, and that the risk of brain changes is increased in people living in areas with a high aluminium content in the drinking water supply. Some of these findings have been criticised, disproved, or not confirmed by other workers. Listed below are some of the studies which point to an association between aluminium intake and Alzheimer's disease,[5-8] some criticisms,[9-13] and some negative findings.[14,15]

There does not appear to be a risk of aluminium accumulation from normal use of aluminium-containing antacids by patients with normal renal function; consequently use of these antacids by such patients should not be considered to put them at risk of Alzheimer's disease.[16,17]

1. Crapper McLachlan DR, *et al.* Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? *Can Med Assoc J* 1991; **145**: 793–804.
2. Anonymous. Is aluminium a dementing ion? *Lancet* 1992; **339**: 713–14.
3. Munoz DG. Is exposure to aluminium a risk factor for the development of Alzheimer disease?—No. *Arch Neurol* 1998; **55**: 737–9.
4. Forbes WF, Hill GB. Is exposure to aluminium a risk factor for the developmem of Alzheimer disease?—Yes. *Arch Neurol* 1998; **55**: 740–1.
5. Martyn CN, *et al.* Geographical relation between Alzheimer's disease and aluminium in drinking water. *Lancet* 1989; **i**: 59–62.
6. Crapper McLachlan DR, *et al.* Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 1991; **337**: 1304–8.
7. Good PF, *et al.* Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study. *Ann Neurol* 1992; **31**: 286–92.
8. Harrington CR, *et al.* Alzheimer's-disease-like changes in tau protein processing: association with aluminium accumulation in brains of renal dialysis patients. *Lancet* 1994; **343**: 993–7.
9. Ebrahim S. Aluminium and Alzheimer's disease. *Lancet* 1989; **i**: 267.
10. Schupf N, *et al.* Aluminium and Alzheimer's disease. *Lancet* 1989; **i**: 267.
11. Lindesay J. Aluminium and Alzheimer's disease. *Lancet* 1989; **i**: 268.
12. Birchall JD, Chappell JS. Aluminium, water chemistry, and Alzheimer's disease. *Lancet* 1989; **i**: 953.
13. Whalley LJ, *et al.* Aluminium and dementia. *Lancet* 1992; **339**: 1235–6.
14. Markesbery WR, *et al.* Instrumental neutron activation analysis of brain aluminum in Alzheimer's disease and aging. *Ann Neurol* 1981; **10**: 511–16.
15. Wettstein A, *et al.* Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. *Int Arch Occup Environ Health* 1991; **63**: 97–103.
16. Anonymous. Aluminium salts and Alzheimer's disease. *Pharm J* 1991; **246**: 809.
17. Flaten TP, *et al.* Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45**: 203–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Podexine Exfoliante.

Multi-ingredient Preparations. *Braz.*: Belagin†; *Chile*: Podexine Anti-Transpirante; *Ital.*: Rino Get; *Mex.*: Dicentril†; Ulgel.

Homoeopathic Preparations. *Fr.*: Abbe Chaupitre no 10†; Abbe Chaupitre no 22†.

Pharmacopoeial Preparations
BP 2014: Compound Aluminium Paste.

Aluminium Acetate

Aluminio, acetato de; Aluminum Acetate; Ацетат Алюминия; Уксуснокислый Алюминий.
$C_6H_9AlO_6$=204.1
CAS — 139-12-8.
UNII — 80EHD8I43D.

Profile

Aluminium acetate is prepared from aluminium sulfate and acetic acid.

Solutions containing aluminium acetate are astringent. Ear drops, which correspond to a solution of aluminium acetotartrate in that they are prepared from aluminium sulfate with the aid of acetic acid and tartaric acid, reduce oedema and inflammation of the ear in conditions such as otitis externa (p. 195.1) by producing an acidic environment hostile to pathogenic bacteria; they are also hygroscopic. Solutions, usually prepared from glacial acetic acid and an aluminum subacetate topical solution (which is itself prepared from aluminium sulfate and acetic acid), have also been used in dermatology as astringent lotions for irritating skin conditions.

Various preparations containing aluminium acetate have been known as Burow's creams, emulsions, lotions, or solutions.

Aluminium acetotartrate and aluminium subacetate (basic aluminium acetate) are also used as topical astringents.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Buro-Sol; *Ger.*: Alsol; Essigsaure Tonerde-Salbe; Essitol; *Hung.*: Alsol; Cremor; *Pol.*: Altacet; Altaziaja; Altix; *Switz.*: Buceta†; *USA*: Bite Rx; *Venez.*: Acid Mantle.

Multi-ingredient Preparations. *Arg.*: Epiprocto†; *Austral.*: Xyloproct; *Austria*: Acetonal†; Nasanal; *Braz.*: Xyloproct; *Fr.*: Gel a l'Acetotartrate d'Alumine Defresne†; *Gr.*: Xyloproct; *Hong Kong*: Haemoral†; *Indon.*: Haemocaine; *Irl.*: Xyloproct†; *Israel*: Proctozorin-N; *Ital.*: Betaderm†; Micofoot; Oleo Calcarea; Vegetallumina; *Malaysia*: Xyloproct; *Mex.*: Dermanol; Litiset; Xyloproct Plus; *Norw.*: Xyloproct†; *NZ*: Xyloproct; *Pol.*: Kamagel; *Rus.*: Kamagel (Камагель); *Spain*: Avril; *Swed.*: Xyloproct; *Switz.*: Euceta avec camomille et arnica; Fenipic; Fortacet†; Mikutan N†; Realderm; Topaceta†; *Turk.*: Hemoralgine; *UK*: Xyloproct; *Ukr.*: Camagel (Камагель); *USA*: Borofair Otic†; Burow's; Otic Domeboro; Star-Otic.

Pharmacopoeial Preparations
BP 2014: Aluminium Acetate Ear Drops;
USP 36: Aluminum Subacetate Topical Solution.

Aluminium Lactate

Aluminio, lactato de; Aluminum Lactate; Алюминия Лактат.
Tris(lactato)aluminium.
$C_9H_{15}AlO_9$=294.2
CAS — 537-02-0; 18917-91-4.
UNII — V797H4GG0Z.

Profile

Aluminium lactate is used in the local treatment of various disorders of the mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Etiaxil; *Ital.*: Aluctyl†.

Multi-ingredient Preparations. *Israel*: Aronal Forte; *Ital.*: Lacalut; *Port.*: Gartun; *Switz.*: Deaftol; Drossadinetten; Drossadinol.

Aluminium Sulfate

Aluminio sulfatas; Alumiinisulfaatti; Aluminii Sulfas; Aluminii Sulfas Hydricus; Aluminio, sulfato de; Aluminium, sulfate d'; Aluminium Sulfuricum; Aluminium Sulphate; Aluminium Trisulphate; Aluminiumsulfat; Alumínium-szulfát; Aluminum Sulfate; E520; Glinu siarczan; Síran hlinitý hydrát; Сульфат Алюминия.
$Al_2(SO_4)_3.xH_2O$=342.1 (anhydrous)
CAS — 10043-01-3 (anhydrous aluminium sulfate); 17927-65-0 (aluminium sulfate hydrate).
UNII — 34S289N54E (aluminium sulfate hydrate); I7T908772F (anhydrous aluminium sulfate).

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

Ph. Eur. 8: (Aluminium Sulfate). Colourless lustrous crystals or crystalline masses. It contains 51 to 59% of $Al_2(SO_4)_3$. Soluble in cold water; freely soluble in hot water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Aluminum Sulfate). Contains 54 to 59% of $Al_2(SO_4)_3$. An odourless, white, crystalline powder, shining plates, or crystalline fragments. Soluble 1 in 1 of water; insoluble in alcohol. The pH of a 5% solution in water is not less than 2.9.

Profile

Aluminium sulfate has an action similar to that of alum (p. 2439.1) but is more astringent. Topical preparations containing 20% aluminium sulfate have been used for the treatment of envenomation by certain insects and marine organisms. The aluminium may cause precipitation of the proteins contained within the venoms thus reducing local toxicity. Aluminium sulfate is also included in astringent preparations intended to soothe irritating skin conditions.

Aluminium sulfate is also used in the preparation of aluminium acetate solutions.

Adverse effects. Possible adverse effects or toxicity associated with aluminium, or aluminium salts such as aluminium sulfate, in the public water supply are discussed under Aluminium, p. 2439.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Stingose; *Hong Kong*: Stingose†; *NZ*: Stingose; *UK*: Stingose.

Multi-ingredient Preparations. *Canad.*: Boropak†; *Mex.*: Domeboro; *USA*: Domeboro; Ostiderm; Pedi-Boro Soak Paks†.

Pharmacopoeial Preparations
USP 36: Aluminum Subacetate Topical Solution; Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution.

Amber Oil

Oleum Succini; Rectified Amber Oil.
CAS — 9000-02-6 (amber); 8002-67-3 (amber oil).

Profile

Amber oil is formed by the destructive distillation of Baltic amber, a fossilised tree resin that contains succinic acid. It has properties and uses similar to those of turpentine oil.

The 'amber oils' used in aromatherapy are generally derived from non-fossilised tree resins or gums mixed with essential oils and other ingredients.

Homoeopathy

Amber has been used in homoeopathic medicines under the following names: Bernstein; Electron; Succinum

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Puma Balm; *UK*: Nine Rubbing Oils; *Ukr.*: Bezornil (Безорнил).

Ambergris

CAS — 8038-65-1 (ambergris); 473-03-0 (ambrein).
UNII — XTC0D02P6C.

Profile

Ambergris is a waxy solid produced in the intestines of sperm whales. It consists mainly of ambrein (a triterpene alcohol), cholesterol, and benzoic acid. Both ambergris and ambrein are used in perfumery.

Homoeopathy

Ambergris has been used in homoeopathic medicines under the following names: ambra grisea; ambre gris.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Ambra Med Complex; Asarum Med Complex; Avena Med Complex; Lobelia Med Complex; Mefem; Relax; Vertigoheel; Vertigopas; *Canad.*: Amphosca†; Biomag†; Men Complex†; *Cz.*: Vertigoheel; *Fr.*: Amphosca Orchitine; Amphosca Ovarine; Biomag; Gastro-Drainol†; Kalium Phosphoricum Complexe No 100; Sepia Complexe No 20; *Ger.*: Ambrax; Infinerval; Manuia; Nervo-Plantin†; Nervoid N; Pascolibrin; Presselin Nervenkomplex; Presselin Nervennahrung N†; Tondinel H; Vertigoheel; Vertigopas; Vertizin; *Hung.*: Vertigoheel; *Neth.*: Acidolite; Cerebrum comp; Homeocare neusspray; Neurovita; Sinufleur; *Rus.*: Sambucus-Plus (Самбухус-Плюс); Valeriana-Plus (Валериана-Плюс); *S.Afr.*: Vertigoheel; *Switz.*: HerBalance; Vertigoheel; *Ukr.*: Homvio-Nervin (Хомвио-Нервин); *USA*: Preferred Remedies Stress; Vertigoheel.

Ambucetamide *(BAN, rINN)*

A-16; Ambucetamida; Ambucétamide; Ambucetamidum; Dibutamide; Амбуцетамид.
2-Dibutylamino-2-(4-methoxyphenyl)acetamide.
$C_{17}H_{28}N_2O_2$=292.4
CAS — 519-88-0.
UNII — 131B408RZI.

Profile

Ambucetamide is an antispasmodic and has been given for the relief of dysmenorrhoea. The hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Neth.*: Femerital†.

Ambutonium Bromide *(BAN)*

Ambutonii Bromidum; Ambutoniumbromid; Ambutoniumbromidi; BL-7008; R-100; Амбутония Бромид.
(3-Carbamoyl-3,3-diphenylpropyl)ethyldimethylammonium bromide.
$C_{20}H_{27}BrN_2O$=391.4
CAS — 14007-49-9 (ambutonium); 115-51-5 (ambutonium bromide).
UNII — 9J8YA3ZT14.

Profile

Ambutonium bromide is a quaternary ammonium antimuscarinic that has been used in gastrointestinal disorders with smooth muscle spasm.

Amilomer (rINN)

Amilomère; Amilómero; Amilomerum; Амиломер.

CAS — 42615-49-6.

Profile

Amilomer consists of microspheres produced by reaction of partially hydrolysed starch with epichlorohydrin, quickly degradable by amylase (with a half-life of less than 120 minutes); the name is followed by a hyphenated numerical code in which the number preceding the hyphen indicates the half-life in minutes and that following the hyphen indicates the mean diameter of the microspheres in µm.

Amilomer is used in transarterial chemoembolisation procedures in the management of hepatic malignancies.

Aminohippuric Acid

Ácido *p*-aminohipúrico; Ácido paraminohipúrico; Acidum Aminohippuricum; *p*-Aminobenzoylglycine; *p*-Aminohippuric Acid; Aminohippurihappo; Aminohippursyra; Aminohipúrico, ácido; Kwas aminohipurowy; PAHA; Para-aminohippuric Acid; Аминогиппуровая Кислота.

N-4-Aminobenzoylaminoacetic acid.

$C_9H_{10}N_2O_3$=194.2

CAS — 61-78-9 (aminohippuric acid); 94-16-6 (sodium aminohippurate).

ATC — V04CH30.

ATC Vet — QV04CH30.

UNII — Y79XT838J9.

Pharmacopoeias. In *US*.

USP 36: (Aminohippuric Acid). A white crystalline powder which discolours on exposure to light. Soluble 1 in 45 of water, 1 in 50 of alcohol, and 1 in 5 of 3N hydrochloric acid; very slightly soluble in carbon tetrachloride, in chloroform, in ether, and in benzene; freely soluble in alkaline solutions with some decomposition, and in diluted hydrochloric acid. Store in airtight containers. Protect from light.

Uses and Administration

Aminohippuric acid is excreted mainly by proximal tubular secretion, with some glomerular filtration. It is given as sodium aminohippurate (aminohippurate sodium; $C_9H_9N_2NaO_3$=216.2) for the estimation of effective renal plasma flow. It is given by intravenous infusion in a suggested priming dose of 6 to 10 mg/kg followed by an infusion dose of 10 to 24 mg per minute to achieve a plasma sodium aminohippurate concentration of 2 mg/100mL; at these concentrations about 90% of aminohippurate is cleared from the renal bloodstream in a single circuit in patients with normal renal function. Sodium aminohippurate has also been used for the assessment of the renal tubular secretory mechanism. Doses for this purpose are infused slowly to achieve a plasma concentration of 400 to 600 micrograms/mL to saturate the tubular secretion. These tests are used mainly in research procedures.

Adverse Effects and Precautions

Sodium aminohippurate may cause nausea and vomiting, hypersensitivity reactions, vasomotor disturbances, flushing, tingling, cramps, and a feeling of warmth. Patients may develop an urge to urinate or defaecate after infusion.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aminohippuric 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 20/10/11)

Interactions

The estimation of sodium aminohippurate may be affected in patients taking procaine, sulfonamides, or thiazosulfone. Probenecid diminishes the excretion of aminohippuric acid. Clearance is also affected by penicillins, salicylates, and other drugs that compete for the same excretory pathways.

Preparations

Pharmacopoeial Preparations

USP 36: Aminohippurate Sodium Injection.

Ammi Visnaga

Bishop's Weed; Biznaga; Kela; Khella; Khellah; Picktooth Fruit; Visnaga; Аммиа зубная (*Ammi visnaga*).

ATC — Herb — HC01DW5001 (Ammi visnaga fruit); HA03WA5001 (Ammi visnaga fruit); HR03WB5001 (Ammi visnaga leaf).

UNII — IZM4T38Q8A (Ammi visnaga); 3UN285QN0C (Ammi visnaga fruit).

NOTE. The name Bishop's Weed is commonly used to refer to the related medicinal herb *Ammi majus*. It is also used for *Aegopodium podagraria* (Apiaceae) (Goutweed, Ground Elder).

Profile

The fruit of *Ammi visnaga* (Apiaceae) is used in herbal preparations. It is also a source of khellin (p. 2538.1) and visnadine (p. 2646.1).

Homoeopathy

Ammi visnaga has been used in homoeopathic medicines under the following names: Ammi vis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Ammifurin (Аммифурин); Avisan (Ависан).

Multi-ingredient Preparations. *Austria*: Urelium Neu; *Ger.*: Cefadrin†; *Pol.*: Kelicardina; Nefrol; *Ukr.*: Flavia (Флавиа); Phytolyt (Фитолит).

Homoeopathic Preparations. *Ger.*: A-Bomin; Asthmakhell N; Cefangipect H†; Cefangipect†; Cefaspasmon N†; Cefavora Cor; Lowe-Komplex Nr 10; Pollinosan†; Pulmo Bronchialcomplex; *Neth.*: Asakell; Asthmakhell†; Holergie; *Switz.*: A Vogel Spray contre le rhume des foins; Pollinosan†.

Ammonia

Amoniaco; solución diluida de; Amonowy wodorotlenek; Amonyak.

CAS — 7664-41-7.

UNII — 5138Q19F1X.

NOTE. The food additive number E527 is used for ammonium hydroxide. Solutions of ammonia in water have been referred to as ammonium hydroxide solutions. Strong solutions of ammonia have also been described by the synonyms Ammoniaca, Ammoniacum, Ammoniaque Officinale, and Liquor Ammoniae Fortis. Dilute solutions of ammonia have also been referred to as Ammonia Water, Ammonium Hydricum Solutum, Liquor Ammoniae, and Liquor Ammoniae Dilutus.

Pharmacopoeias. Strong ammonia solutions are included in *Chin.* (25 to 28%), *Eur.* (see p. vii) (25 to 30%), and *USNF* (27 to 31%). Dilute ammonia solutions are included in *Br.*, *Chin.*, *Ger.*, *Jpn*, and *Swiss* (all about 10%).

Ph. Eur. 8: (Ammonia Solution, Concentrated; Ammoniae Solutio Concentrata; Strong Ammonia Solution BP 2014). It contains between 25% and 30% (w/w) of ammonia, NH_3. A clear colourless liquid. Very caustic. Miscible with water and with alcohol. Store at a temperature not exceeding 20 degrees in airtight containers.

BP 2014: (Dilute Ammonia Solution). It is prepared by diluting Strong Ammonia Solution with freshly boiled and cooled purified water. It contains 9.5 to 10.5% w/w of NH_3.

NOTE. The BP directs that when Ammonia Solution is prescribed or demanded, Dilute Ammonia Solution shall be dispensed or supplied.

USNF 31: (Strong Ammonia Solution). It contains between 27% and 31% (w/w) of NH_3. On exposure to air, it loses ammonia rapidly. A clear colourless liquid with an exceedingly pungent characteristic odour. Store at a temperature not exceeding 25 degrees in airtight containers.

Handling. Strong ammonia solutions should be handled with great care because of the caustic nature of the solutions and the irritating properties of the vapour. Cool the container well before opening and avoid inhalation of the vapour.

Uses and Administration

Dilute solutions of ammonia have been used as reflex stimulants either as smelling salts or oral solutions. They have also been used as rubefacients and counter-irritants (see p. 6.3) and to neutralise insect stings. Users should always be aware of the irritant properties of ammonia.

Hartshorn and Oil was sometimes used as a name for an ammonia liniment. Household ammonia and cloudy ammonia have been used as names for cleaning preparations of ammonia with oleic acid or soap respectively. A saturated solution containing about 35% w/w and known as '0.880 ammonia' has been used in many chemical and industrial applications.

Stings. Bathers who were stung by Portuguese men-of-war (*Physalia physalis*) were rapidly and effectively relieved of discomfort, paresis, irritation, and other symptoms by the application of aromatic ammonia spirit compresses.[1]

1. Prohman IG. Treatment of physalia stings. *JAMA* 1966; 197: 733.

Adverse Effects

Ingestion of strong solutions of ammonia causes severe pain in the mouth, throat, and gastrointestinal tract, as well as severe local oedema and salivation, with cough, vomiting, and shock. Burns to the oesophagus and stomach may result in perforation. Stricture formation, usually in the oesophagus, can occur weeks or months later. Ingestion may also cause oedema of the respiratory tract and pneumonitis, though this may not develop for a few hours.

Inhalation of ammonia vapour causes sneezing and coughing and in high concentration causes pulmonary oedema. Asphyxia has been reported after oedema or spasm of the glottis. Ammonia vapour is irritant to the eyes and causes weeping; there may be conjunctival swelling and temporary blindness.

Ammonia solution in contact with skin and eyes produces blistering and vesiculation; ammonia burns feel 'soapy' because of saponification of the tissues. Strong solutions on the conjunctiva cause a severe reaction with conjunctival oedema, corneal damage, and acute glaucoma. Late complications include angle-closure glaucoma, opaque corneal scars, atrophy of the iris, and formation of cataracts. Ammonia burns have resulted from treating insect bites and stings with the strong solution, and even with the dilute solution, especially if a dressing is subsequently applied.

References.

1. Beare JDL, *et al.* Ammonia burns of the eye: an old weapon in new hands. *BMJ* 1988; 296: 590.
2. WHO. Ammonia health and safety guide. *IPCS Health and Safety Guide 37.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/hsg/hsg/hsg037.htm (accessed 04/04/06)
3. Payne MP, Delic JL. Ammonia. In: *Toxicity Review 34.* London: HMSO, 1991: 1–12.
4. Payne MP, *et al.* *Toxicology of substances in relation to major hazards: ammonia.* London: HMSO, 1991.
5. Leduc D, *et al.* Acute and long term respiratory damage following inhalation of ammonia. *Thorax* 1992; 47: 755–7.
6. Michaels RA. Emergency planning and the acute toxic potency of inhaled ammonia. *Environ Health Perspect* 1999; 107: 617–27.
7. Amshel CE, *et al.* Anhydrous ammonia burns case report and review of the literature. *Burns* 2000; 26: 493–7.
8. Kerstein MD, *et al.* Acute management of exposure to liquid ammonia. *Mil Med* 2001; 166: 913–14.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing ammonia-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p. 1769.2.

Treatment of Adverse Effects

Ingestion of ammonia solutions should not be treated by lavage or emesis. Milk or water have been given as diluents, but small volumes should be used to reduce the risk of inducing emesis. Appropriate measures should be taken to alleviate pain, shock, and pulmonary oedema, and maintain an airway.

Contaminated skin and eyes should be flooded immediately with water and the washing continued for at least 15 minutes. Any affected clothing should be removed while flooding is being carried out.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: After Bite†; *Irl.*: After Bite; *Israel*: Afterbite; *Spain*: After Bite; Calmapica; Goipic; *Switz.*: After Bite; *UK*: After Bite.

Multi-ingredient Preparations. *Austral.*: Senega and Ammonia; *Austria*: Rowalind; *Canad.*: Calmapic†; SJ Liniment†; *Chile*: Rhus Opodeldoc; *Fr.*: Hypneine†; Lipothymal†; *Irl.*: Blistex Relief; *Ital.*: Activ Dopo Puntura†; Baby Zanzara†; *Rus.*: Pectorales Elixir (Грудной Эликсир); *S.Afr.*: Enterodyne†; *Spain*: Masagil†; *UK*: Blistex Relief; Goddards Embrocation; Mackenzies Smelling Salts; Pickles Smelling Salts; *USA*: Emergent-Ez.

Homoeopathic Preparations. *Austral.*: Respatona Sore Throat.

Pharmacopoeial Preparations

BP 2014: Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment.

Ammonium Citrate

Ammon. Cit.; Amonowy cytrynian; E380; Triammonium Citrate; Цитрат Аммония.

$C_6H_5O_7(NH_4)_3$=243.2

CAS — 3458-72-8.

UNII — J90A52459R.

Profile

Ammonium citrate is used as a food additive and has been used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Ambrotos; Mucobrol; *India*: HB Rich.

Ammonium Phosphate ⊗

545 (ammonium polyphosphates); Amonowy wodorofosforan; Diammonium Hydrogen Phosphate; Dibasic Ammonium Phosphate; Fosfato de amonio; Фосфат Аммония.

Diammonium hydrogen orthophosphate.

$(NH_4)_2HPO_4$=132.1

CAS — 7783-28-0.

UNII — 10LGE70FSU.

Pharmacopoeias. In *USNF*.

USNF 31: (Ammonium Phosphate). Colourless or white granules or powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 7.6 to 8.2. Store in airtight containers.

Profile

Ammonium phosphate was formerly used as a diuretic. It may be used as a buffering agent in pharmaceutical preparations.

Ammonium biphosphate (monobasic ammonium phosphate; $NH_4H_2PO_4$=115.0) has been used to acidify urine and as a phosphate supplement.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Phosphore Alko; *Pol.*: Phosphor†.

Homoeopathic Preparations. *Chile*: Ikoplex No 5; *Ger.*: Girheulit HM†; Girheulit HOM; Rufebran rheumo†.

Amnion

Amnios; Амнион.

Profile

Human extra-embryonic fetal membranes comprise an inner amniotic membrane, the amnion, and an outer membrane, the chorion. Amnion is used in ocular surgery for a range of conditions. Both amnion and combined membranes have been used as a dressing for raw wounds including chronic ulcers and burns.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: FegaCoren.

Homoeopathic Preparations. *Ger.*: Neydin-F†; Neydin-M†; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A.

Amylase

Amilasa; Amylaza; Diastasa; Diastase; EC 3.2.1.1 (α-amylase); EC 3.2.1.2 (β-amylase); EC 3.2.1.3 (glucoamylase); Glucogenasa; Glucogenase; Ptialina; Ptyalin; Амилаза.

CAS — 9000-92-4 (amylase); 9000-85-5 (bacterial α-amylase); 9000-90-2 (porcine α-amylase, pancreatic); 9001-19-8 (taka-diastase); 9000-91-3 (β-amylase); 9032-08-0 (glucoamylase).

ATC — A09AA01.

ATC Vet — QA09AA01.

UNII — I909J9CFAT (α-amylase a type-1/2).

Pharmacopoeias. In *Fr.* and *Jpn*.

Uses and Administration

The term amylase refers to an enzyme catalysing the hydrolysis of α-1,4-glucosidic linkages of polysaccharides such as starch, glycogen, or their degradation products. Amylases may be classified according to the manner in which the glucosidic bond is attacked. Endoamylases attack the α-1,4-glucosidic linkage at random. Alpha-amylases are the only types of endoamylases known and yield dextrins, oligosaccharides, and monosaccharides. The more common alpha-amylases include those isolated from human saliva, mammalian pancreas, *Bacillus subtilis*, *Aspergillus oryzae*, and barley malt. Exoamylases attack the α-1,4-glucosidic linkage only from the non-reducing outer polysaccharide chain ends. They include beta-amylases and glucoamylases (amyloglucosidases or gamma-amylases) and are of vegetable or microbial origin. Beta-amylases yield beta-limit dextrins and maltose, and glucoamylases yield glucose.

Amylase is used in the production of predigested starchy foods and for the conversion of starch to fermentable sugars in the baking, brewing, and fermentation industries.

Amylase from various sources has been used as an ingredient of preparations of mixed digestive enzymes, and has been given orally for its supposed activity in reducing respiratory-tract inflammation and local swelling and oedema. Pancreatic enzymes such as pancreatin (p. 2579.3) and pancrelipase (p. 2580.1) have amylase activity.

Adverse Effects

Hypersensitivity reactions have been reported.

Hypersensitivity. References to asthma developing after occupational exposure to amylases used in the flour milling[1-3] and detergent[4,5] manufacturing industries, and studies[6-8] to assess the likelihood of developing amylase hypersensitivity after ingesting wheat products including bread.

1. Smith TA, *et al.* Respiratory symptoms and wheat flour exposure: a study of flour millers. *Occup Med (Lond)* 2000; 50: 25–9.
2. Cullinan P, *et al.* Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers: a case-control analysis. *Ann Occup Hyg* 2001; 45: 97–103.
3. Quirce S, *et al.* Glucoamylase: another fungal enzyme associated with baker's asthma. *Ann Allergy Asthma Immunol* 2002; 89: 197–202.
4. Bole AM, *et al.* Occupational asthma caused by bacillary amylase used in the detergent industry. *Occup Environ Med* 2000; 57: 840–2.
5. Cullinan P, *et al.* An outbreak of asthma in a modern detergent factory. *Lancet* 2000; 356: 1899–1900.
6. Cullinan P, *et al.* Clinical responses to ingested fungal alpha-amylase and hemicellulase in persons sensitized to Aspergillus fumigatus? *Allergy* 1997; 52: 346–9.
7. Sander I, *et al.* Is fungal alpha-amylase in bread an allergen? *Clin Exp Allergy* 2000; 30: 560–5.
8. Simonato B, *et al.* IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001; 31: 1771–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Orenzym; *Fr.*: Flaviastase†; Maxilase; Megamylase; Oromylase†; *India*: Galazyme-Pro; *Mon.*: Amylodiastase; *Port.*: Maxilase.

Multi-ingredient Preparations. *Arg.*: Docechol; Dom-Pollenzim; Gastridin-E; Homocisteon Compuesto; Pakinase; Pollenzim; Tridigestivo Soubeiran; *Austral.*: Enzyme; Vegie Digestaid; *Austria*: Wobenzym; *Belg.*: Digestomen; *Braz.*: Essen; Peptopancreasi†; Primeral; Thiomucase; *Canad.*: Digesdyn; Digesta; Digestolax; Dipan†; Multi-Zyme†; Pancre Zyme†; Synergy Defense; *Chile*: Flapex E; *China*: Dages (达吉); Wei Tai Kang (调泰康); YiMei (怡美); *Cz.*: Wobenzym; *Hong Kong*: Appezym; Bio-Tomosan†; Caricose†; Digezym; Enzyme Co†; Enzyplex; Magesto; Uni-Paptase†; *India*: Afizyme; Aglozyme; Aglozyme; Aldezyme; Alzyme; Aniwel DPS; Anzykair; Anzykair; Aquadil-P; Aristozyme; Arizyme; Asizyme; Astozyme; Atopep; Bactzyme; Bestozyme P; Bestozyme; Bestozyme; Biota-P; Biozyme; Canzyme; Cascazyme; Catalyd; Catazyme-P; Catazyme; Daffozyme; Dewzym; Digems-CT; Digeplex-T; Digeplex; Digeplex; Digestomen-P; Digitage; Dipep; Dipep; Disnizyme; Dorzy DPS; Dorzy; Duozyme; E-Pep; Eaze; Elfazyme; Endos; Entozyme; Entrozyme; Enzar; Enzofast; Enzofast; Enzytel; Estzyme; Everzyme; Extrazyme; Farizym; Ferizyme; Fozyme; Fullzyme; Fyzyme; Gaskit; Gaskit; Gastrofit; Gastrozyme; Gastrozyme; Genozyme; Genozyme; Glozyme; Hanzyme; HG Zyme; Ifyzyme; Indozyme; Infazyme; Intazyme; Intazyme; Intrazyme Tonic; Intrazyme; Jayzyme; Kairase; Kamozyme; KDZyme; Kingzyme; Lac-B; Lavazyme; Lavazyme; Laxzyme; Leno-EZ; Litzyme; Lupizyme; Lyzyme; M-Zyme; Maprazyme; Martiz; Merozyme-C; NBGest; Nectozyme; Neopeptine; Neopeptine; Neopeptine; Nifazyme; Novazyme Elachi; Nutrozyme; Nutrozyme; Nutrozyme; Onazyme; Optizyme; Panzyme; Papytazyme; PP Bio; PP Tage; Sanzyme-DS; Unienzyme; Unienzyme; Vitazyme; Vitazyme; *Indon.*: Aludonna; Enzyplex; Excelase-E; Librozym Plus†; Librozym†; Vitazym; Xepazym; *Jpn*: Cabagin†; *Malaysia*: Biotase; Enzyme Digest; Enzyplex†; Pepfix; *Mex.*: Ochozim; Wobenzym; Zimotris; *Port.*: Modulanzime; *Rus.*: Pepfiz (Пепфиз); Unienzyme с MPS (Юнизим с МПС); Wobenzym (Вобэнзим); *Singapore*: Biotase; Enzyplex; Weisen-U; *Spain*: Demusin†; Digestomen Complex; *Thail.*: Corisul; Diasgest; Digestin; Enzyplex†; Flataco; Flatulence†; Magesto; Mesto-OI; Patarsul; Pepfix; Pepsitase; Polyenzyme-I†; *UK*: Enzyme Digest; Enzyme Plus; *Ukr.*: Wobenzym (Вобэнзим); *USA*: Bio-Zyme; Digex†; Enzyme; Ku-Zyme†; Kutrase†; Papaya Enzyme; Similase Jr; *Venez.*: Festal Reformulado.

Anagrelide Hydrochloride *(BANM, USAN, rINNM)*

Anagrelida, hidrocloruro de; Anagrélide, Chlorhydrate d'; Anagrelidi Hydrochloridum; BL-4162a; BMY-26538-01; Hidrocloruro de anagrelida; Анагрелида Гидрохлорид.

6,7-Dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3*H*)-one hydrochloride.

$C_{10}H_7Cl_2N_3O,HCl$=292.5

CAS — 68475-42-3 (anagrelide); 58579-51-4 (anagrelide hydrochloride); 823178-43-4 (anagrelide hydrochloride monohydrate).

ATC — L01XX35.

ATC Vet — QL01XX35.

UNII — VNS4435G39 (anagrelide hydrochloride); YTM763Y5C8 (anagrelide hydrochloride monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Anagrelide Hydrochloride). An off-white to pale pinkish powder. Very slightly soluble in water; sparingly soluble in dimethyl sulfoxide and dimethylformamide. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III that reduces platelet production and, at higher than therapeutic doses, inhibits platelet aggregation. It is used to treat primary (essential) thrombocythaemia (p. 695.2) in patients intolerant of, or unresponsive to, other therapy, and also in thrombocythaemia secondary to other myeloproliferative disorders.

Anagrelide is given orally as the hydrochloride monohydrate ($C_{10}H_7Cl_2N_3O,HCl,H_2O$=310.6) but doses are expressed in terms of the base; 1.2 mg of anagrelide hydrochloride monohydrate is equivalent to about 1 mg of anagrelide. The initial dose is the equivalent of anagrelide 1 mg daily in 2 divided doses. After at least a week, the dose is adjusted, by increasing the daily dose by not more than 500 micrograms in any one week, until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily. The dose should not exceed 10 mg daily or 2.5 mg as a single dose. In the USA, a higher initial dose of 2 mg daily, divided into 2 or 4 doses, is used. For doses to be used in children and in patients with hepatic impairment, see below.

The effects of anagrelide therapy must be regularly monitored: platelet counts should be measured every 2 days during the first week of treatment and then at least weekly until the maintenance dose is reached.

References.

1. Spencer CM, Brogden RN. Anagrelide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia. *Drugs* 1994; 47: 809–22.
2. Chintagumpala MM, *et al.* Treatment of essential thrombocythemia with anagrelide. *J Pediatr* 1995; 127: 495–8.
3. Oertel MD. Anagrelide, a selective thrombocytopenic agent. *Am J Health-Syst Pharm* 1998; 55: 1979–86.
4. Lackner H, *et al.* Treatment of children with anagrelide for thrombocythemia. *J Pediatr Hematol Oncol* 1998; 20: 469–73.
5. Pescatore SL, Lindley C. Anagrelide: a novel agent for the treatment of myeloproliferative disorders. *Expert Opin Pharmacother* 2000; 1: 537–46.
6. Dingli D, Tefferi A. Anagrelide: an update on its mechanisms of action and therapeutic potential. *Expert Rev Anticancer Ther* 2004; 4: 533–41.
7. Steurer M, *et al.* Anagrelide for thrombocytosis in myeloproliferative disorders: a prospective study to assess efficacy and adverse event profile. *Cancer* 2004; 101: 2239–46.
8. Wagstaff AJ, Keating GM. Anagrelide: a review of its use in the management of essential thrombocythaemia. *Drugs* 2006; 66: 111–31.
9. Christoforidou A, *et al.* Hydroxyurea and anagrelide combination therapy in patients with chronic myeloproliferative diseases resistant or intolerant to monotherapy. *Acta Haematol (Basel)* 2008; 120: 195–8.
10. Emadi A, Spivak JL. Anagrelide: 20 years later. *Expert Rev Anticancer Ther* 2009; 9: 37–50.

Administration in children. The recommended initial daily dose of anagrelide in children aged 7 years and over is 500 micrograms orally for one week followed by adjustment of the daily dose in increments of 500 micrograms at weekly intervals until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily; the dose should not exceed 10 mg daily or 2.5 mg as a single dose.

Administration in hepatic impairment. UK licensed product information recommends that anagrelide should not be given to patients with moderate or severe hepatic impairment. In the USA, anagrelide therapy is not recommended in patients with severe hepatic impairment, although patients with moderate hepatic impairment have been given anagrelide in an initial oral daily dose of 500 micrograms, which should be maintained for a minimum of 1 week and with cardiovascular monitoring; the daily dose may then be increased cautiously as above.

Adverse Effects

Adverse effects most commonly reported with anagrelide include headache, palpitations and tachycardia, fluid retention, diarrhoea, nausea, and abdominal pain; fatigue, dizziness, flatulence, vomiting, dyspnoea, rashes, and anaemia have also occurred. Cardiovascular effects also include vasodilatation and positive inotropic effects; myocardial infarction, cardiomyopathy and heart failure have been reported. Anagrelide has been shown to be embryotoxic and fetotoxic in *animal* studies.

Effects on the heart. High-output heart failure occurred in a patient given anagrelide for essential thrombocytosis.[1] Clinical and haemodynamic adverse effects resolved almost immediately on stopping anagrelide.

1. Engel PJ, *et al.* High-output heart failure associated with anagrelide therapy for essential thrombocytosis. *Ann Intern Med* 2005; 143: 311–13.

Effects on the lungs. Severe life-threatening hypersensitivity pneumonitis has been associated with anagrelide.[1]

1. Raghavan M, *et al.* Severe hypersensitivity pneumonitis associated with anagrelide. *Ann Pharmacother* 2003; 37: 1228–31.

Erectile dysfunction. Erectile dysfunction associated with anagrelide therapy has been reported in a patient.[1]

1. Braester A, Lever B. Anagrelide-induced erectile dysfunction. *Ann Pharmacother* 2002; 36: 1291.

Precautions

Anagrelide is mainly removed from the body by hepatic metabolism, and its use is contra-indicated in patients with severe hepatic impairment. In the UK it is additionally contra-indicated in those with moderate impairment, but in the USA its use is permitted in such patients at reduced doses (see p. 2442.3). Licensed product information in the UK also contra-indicates its use in those with moderate to severe renal impairment (creatinine clearance less than 50 mL/minute).

Anagrelide should be used with caution in patients with cardiovascular disease. Cardiac function should be assessed in patients before and during treatment, and patients monitored for cardiovascular adverse effects during treatment. For precautions in patients taking anagrelide with aspirin, see Interactions, below.

Platelet counts should be monitored closely, especially at the start of treatment (see Uses and Administration, p. 2442.3). Haemoglobin, white blood cells, and hepatic and renal function should also be monitored until a maintenance dose is established.

Dizziness may affect the performance of skilled tasks such as driving.

Anagrelide should not be used during pregnancy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anagrelide 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 06/10/11)

Interactions

There is the theoretical possibility that inhibitors of the cytochrome P450 isoenzyme CYP1A2 could reduce the clearance of anagrelide. Anagrelide itself has limited inhibitory activity towards CYP1A2. Anagrelide may exacerbate the effects of other phosphodiesterase inhibitors such as amrinone, cilostazol, enoximone, milrinone, and olprinone that also produce positive inotropic effects.

Potentiation of the effects of other drugs that modify platelet function when given with anagrelide is a theoretical possibility. Although no clinically significant effects have been seen when given with aspirin to patients with essential thrombocythaemia, enhancement of antiplatelet aggregation effects of anagrelide and aspirin has been reported in a study after co-administration to healthy subjects compared with aspirin alone. The UK manufacturers consequently recommend that before starting concomitant treatment of these 2 drugs, the potential risks should be assessed in patients with a high-risk profile for haemorrhage.

Pharmacokinetics

Anagrelide is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 hour after an oral dose on an empty stomach, increasing in the presence of food, although this appears to have no clinically significant effect on bioavailability. It is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP1A2, and eliminated in the urine; less than 1% of a dose is excreted unchanged. The plasma half-life is about 1.3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agrelid; *Austral.*: Agrylin; *Austria*: Thromboreductin; *Belg.*: Xagrid; *Canad.*: Agrylin; *Cz.*: Thromboreductin; Xagrid; *Denm.*: Xagrid; *Fin.*: Xagrid; *Fr.*: Xagrid; *Ger.*: Xagrid; *Gr.*: Agrylin†; Xagrid; *Hong Kong*: Agrylin; Thromboreductin; *Hung.*: Thromboreductin; *Indon.*: Agrylin; Thromboreductin; *Irl.*: Xagrid; *Israel*: Agrylin; Anagrid; *Ital.*: Xagrid; *Malaysia*: Thromboreductin; *Neth.*: Xagrid; *Norw.*: Xagrid; *Philipp.*: Agrylin; *Pol.*: Xagrid; *Port.*: Xagrid; *S.Afr.*: Agrylin; Thromboreductin; *Singapore*: Agrylin†; *Spain*: Xagrid; *Swed.*: Xagrid; *Switz.*: Thromboreductin; Xagrid; *Thai.*: Agrylin; Thromboreductin; *Turk.*: Thromboreductin; *UK*: Xagrid; *USA*: Agrylin.

Pharmacopoeial Preparations
USP 36: Anagrelide Capsules.

Andrographis

Chuanxinlian; Kalmegh; Kariyat; Kirayat.
CAS — 5508-58-7 (andrographolide).
ATC Herb — HA05BA500J (Andrographis paniculata: herb); HN02BG5002 (Andrographis paniculata: herb).
UNII — 0P49L952WZ.

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

USP 36: (Andrographis). Andrographis is the dried stems and leaves of *Andrographis paniculata* (Acanthaceae). It contains not less than 1% of diterpene lactones calculated on the dried basis, as the sum of andrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, and andrograpanin. Protect from light and moisture.

Profile

Andrographis is the dried entire plant or leaves and shoots of *Andrographis paniculata* (Acanthaceae). It has been used as a traditional herbal medicine in Asia. Andrographolide is one of its main constituents.

General references.

1. WHO. Herba Andrographidis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/4.html (accessed 05/02/10)

Respiratory-tract infections. References to the use of andrographis in upper respiratory-tract infections.

1. Coon JT, Ernst E. Andrographis paniculata in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy. *Planta Med* 2004; 70: 293–8.
2. Poolsup N, *et al.* *Andrographis paniculata* in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2004; 29: 37–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cold Combat; *Canad.*: Restorin; *Thai.*: Fa-Thalai-Chon.

Multi-ingredient Preparations. *Austral.*: Andrographis Complex; Andrographis Compound; Echinacea Royale; Gartech†; Immune Boost with Andrographis; *Fr.*: Lactibiane Defenses; *Hung.*: Livfit; *India*: Agloliv; Agloliv; Cytozen; Hepaliv; Hipato-P; Li-Verve; Livasa; Livasa; Livomyn; Livomyn; Livosil-H; Livotone; Livto; Liyurto; Megacure-DS; *Indon.*: Neoboost; *Ital.*: Anglovein; *Philipp.*: Bo-D-Fense†; *Rus.*: Dipana (Дипана); *Singapore*: Hemoglo; *Ukr.*: Detoxopirol (Детоксопирол).

Anecortave *(rINN)*

AL-3789; Anecortava; Anécortave; Anecortave Acetate (USAN); Anecortavum; Анекортав.
17,21-Dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate.
$C_{23}H_{30}O_5$=386.5
CAS — 7753-60-8.
ATC — S01LA02.
ATC Vet — QS01LA02.
UNII — Y0PC411K4T.

NOTE. The name Retaane has been used as a trade mark for anecortave.

Profile

Anecortave is an angiostatic cortisene under investigation for the treatment of patients with neovascular (wet) age-related macular degeneration (p. 880.2). It is similar in structure to cortisol acetate but without any glucocorticoid activity and is able to inhibit several steps of the neovascularisation process. It is given by posterior juxtascleral depot injection and is available in some countries for compassionate use on a named-patient basis.

References.

1. Clark AF. Mechanism of action of the angiostatic cortisene anecortave acetate. *Surv Ophthalmol* 2007; 52 (suppl 1): S26–S34.
2. Regillo CD, *et al.* Clinical safety profile of posterior juxtascleral depot administration of anecortave acetate 15 mg suspension as primary therapy or adjunctive therapy with photodynamic therapy for treatment of wet age-related macular degeneration. *Surv Ophthalmol* 2007; 52 (suppl 1): S70–S78.
3. Russell SR, *et al.* Anecortave acetate for the treatment of exudative age-related macular degeneration—a review of clinical outcomes. *Surv Ophthalmol* 2007; 52 (suppl 1): S79–S90.
4. Geltzer A, *et al.* Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/04/08).
5. Robin AL, *et al.* Reduction of intraocular pressure with anecortave acetate in eyes with ocular steroid injection-related glaucoma. *Arch Ophthalmol* 2009; 127: 173–8.

Anethole

Anethol; Anetol; *p*-Propenylanisole; Анетол.
(*E*)-1-Methoxy-4-(prop-1-enyl)benzene.
$C_{10}H_{12}O$=148.2
CAS — 104-46-1; 4180-23-8 (E isomer).
UNII — Q3JEK5DO4K (natural anethole); A79C64YD3Q (synthetic anethole).

NOTE. Distinguish from Anethole Trithione (below).

Pharmacopoeias. In *Ger.* Also in *USNF.*

USNF 31: (Anethole). Obtained from anise oil or other sources or prepared synthetically. At or above 23 degrees anethole is a colourless or faintly yellow liquid with a sweet taste and the aromatic odour of aniseed. Very slightly soluble in water; soluble 1 in 2 by volume of alcohol; readily miscible with chloroform and with ether. Store in airtight containers. Protect from light.

Profile

Anethole has similar properties to those of anise oil (p. 2444.3). It is also included in mixed terpene preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Rowatinex; *Austria*: Rowatinex; Wick Erkältungssirup für die Nacht; *Canad.*: Bronco Asmol†; *Chile*: Rowatinex; *Cz.*: Rowatinex; *Ger.*: Rowatinex; *Hong Kong*: Neo-Rowatinex; Rowatinex; *Hung.*: Rowatinex; *Indon.*: Listerine Coolmint†; *Irl.*: Rowatinex; *Israel*: Rowatinex; *Malaysia*: Rowatinex; *Philipp.*: Listerine Coolmint; Rowatinex; *Pol.*: Rowatinex; *Rus.*: Rowatinex (Розатинекс); *Spain*: Pulmofasa; Rowanefrin; *Thai.*: Rowatinex; *Ukr.*: Angi Sept Dr Theiss (Анги Септ Др Тайос); *Venez.*: Rowatinex.

Anethole Trithione

Anethole Dithiolthione; Anetheltrithion; Anetol tritiona; SKF-1717; Trithioparamethoxyphenylpropene; Анетона Тритион.
5-(4-Methoxyphenyl)-3*H*-1,2-dithiole-3-thione.
$C_{10}H_8OS_3$=240.4
CAS — 532-11-6.
ATC — A16AX02.
ATC Vet — QA16AX02.
UNII — QUY32964DJ.

NOTE. Distinguish from Anethole (above).

Profile

Anethole trithione has been given orally in the management of dry mouth (p. 2175.3) and as a choleretic. The usual daily dose is 75 mg generally in 3 divided doses before meals. Anethole trithione may cause discoloration of the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Sulfarlem; *Canad.*: Sialor; *China*: Zhengrui (正瑞); *Fr.*: Sulfarlem; *India*: Hepasulfol; *Switz.*: Sulfarlem; *Turk.*: Sulfarlem.

Multi-ingredient Preparations. *India*: Hepasulfol-AA.

Angelica

Andělikový kořen; Angélica; Angelicae Archangelicae Radix; Angelicae radix; Angelikarot; Angélique, racine d'; Angyalgyökér; Archangelica; Archangelicae Radix; Korzeń arcydzięgla; Šventagaršvių šaknys; Väinönputkenjuuri; Ангелика; Дудник.
CAS — 8015-64-3 (angelica oils).
ATC Herb — HG04BW5003 (Angelica archangelica: root); HA03AW5003 (Angelica archangelica: root); HR05YA5002 (Angelica archangelica: root).
UNII — 3W51R3EK30 (Angelica acutiloba root); DTN01M69SN (Angelica archangelica root); 0MF1EI01KJ (Angelica pubescens root).

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

Jpn has separate monographs for *Angelica acutiloba* (Japanese Angelica) and *A. dahurica.*

Chin. specifies *A. dahurica, A. dahurica* var. *formosana, A. pubescens,* and *A. sinensis.*

Ph. Eur. 8: (Angelica Archangelica Root). The whole or cut, carefully dried rhizome and root of *Angelica archangelica* (*Archangelica officinalis*) containing a minimum of 0.2% v/w of essential oil, calculated with reference to the dried drug.

Profile

Angelica (*Angelica archangelica*) is widely used in herbal medicine. The root is used as a bitter to stimulate the appetite. Angelica also has diaphoretic and expectorant properties and has been used for circulatory and respiratory disorders.

Angelica oil is used in aromatherapy.

Angelica contains furanocoumarins and may cause photosensitivity reactions or interfere with anticoagulant therapy.

Other *Angelica* spp. that are used in herbal medicine include *A. acutiloba* (Japanese angelica), *A. dahurica*, *A. pubescens*, and *A. sinensis* (see Dong Quai, p. 2497.1).

Angelica stems are candied for culinary use.

Homoeopathy

Angelica has been used in homoeopathic medicines under the following names: Archangelica; Angelica archangelica; Angelica archangelica var. archangelica.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Sigmafem; Wunderbalsam; *Austral.*: Irontona†; Toxicol; Vitatona†; *Austria*: Abdomilon N; Iberogast; Klosterfrau Melissengeist; Pervivo; *Belg.*: Eau Des Carmes; *Canad.*: Formula T4†; *Cz.*: Dr Theiss Schweden Kräuter†; Dr Theiss Schwedenbitter†; Iberogast; Klosterfrau Melisana; Original Schwedenbitter; Stomaran; Valofyt Neo†; *Fr.*: Boribel Tisane No 6†; Boribel Tisane No 7†; Dystolise; Mediflor Digestive No 3; NurAiD; Santane C_4†; Tigre de Chine; *Ger.*: Abdomilon N; Gastritol; Iberogast; Infi-tract V; Klosterfrau Melissengeist; Melissengeist; Schwedentrunk Elixier; *Hung.*: Antipoll; Bano Svedkeseru; Bittner; Iberogast; Klosterfrau Melisana; *Ital.*: Florelax; *Jpn*: Bofutsushosan; Choreitogoshimotsuto; Daibofuto; Gorinsan; Hochuekkito; Jiinkokato; Jiinshihoto; Junchoto; Juzentaihoto; Kamikihito; Kamishoyosan; Keigairengyoto; Kihito; Kyukikyogaito; Ninjin'yoeito; Nyoshinsan; Otsujito; Ryutanshakanto; Saikoseikanto; Seihaito; Seishoekkito; Shichimotsukokato; Shimotsuto; Shiunko; Shofusan; Sokeikakketsuto; Toktinshi; Tokikenchuto; Tokishakuyakusan; Tokishigyakukagoshuyushokyoto; Tokito; Tsudosan; Unkeito; Unseiin; Yokuininto; Yokukansan; Yokukansankachimpihange; *Neth.*: Iberogast; *Philipp.*: BSI Medicated Plaster; Hemofer; Zilongjin; *Pol.*: Iberogast; Melis-Tonic; Melisal; Melisana Klosterfrau; Melissed; Nervosol; Pervivo; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Wantong Artiplas (Ванытуг Артиплас); *S.Afr.*: Melissengeist†; Spiritus Contra Tussim Drops†; *Spain*: Agua del Carmen; Iberogast; *Swed.*: Iberogast; *Switz.*: Gastrosan; Iberogast; *UK*: Digestion Calming Drops; Melissa Comp.; *Ukr.*: Gastritol (Гастритол); Huato Pills (Бопосы Хуато); Iberogast (Иберогаст); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; *USA*: Mucotrol.

Homoeopathic Preparations. *Switz.*: Regenaplex Nr 28a; Regenaplex Nr 41a; Regenaplex Nr. 3; *UK*: Cough Drops.

Animal Tissue Extracts

Mammalian Tissue Extracts

Mamíferos, extractos tisulares; Экстракты из Млекопитающей Ткани.

Profile

Many medicinal preparations with definite pharmacological activity and valid clinical uses are of mammalian origin and are described under their appropriate monographs—for example, calcitonin, corticotropin, hydrocortisone (cortisol), some enzymes, heparin, insulin, parathyroid hormone, pituitary hormones, some sex hormones, and thyroid.

Other preparations of animal origin have been promoted for various disorders. Evidence of pharmacological activity is generally lacking and such preparations are often of doubtful benefit.

Homoeopathy

Animal tissues that have been used in homoeopathic preparations include the following: Anas Barbariae Hepatis et Cordis; Bufo Bufo; Cerebellum; Diencephalon; Gingiva Bovis; Pituitary Gland; Sus Scrofa Umbilical Cord; Tonsillae Palatinae Bovis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Raw Prostate; Renacenz; Sigmatrofic; Solcoseryl; *Austria*: Actovegin; Cerebrolysin; Enzynorm; Solcoseryl; *Chile*: Renacenz; *China*: Actovegin (爱维治); Ao De Jin (奥德金); Cerebrolysin (脑活素); Pu Ke Tuo (复可托); Hong Yuan (鸿源); Lang Du (朗度); Sheng Qi (生祺); Shuai Qi (帅奇); Xin Ou Rui (新欧瑞); Xin Wei Zhi (欣维治); *Cz.*: Cerebrolysin; Solcoseryl; *Fr.*: Eurobiol; *Ger.*: Actihaemyl; Actovegin†; Cerebrolysin†; *Gr.*: Actovegin; Solcoseryl; *Hong Kong*: Actovegin; Cerebrolysin; Leviden†; Solcoseryl; *Hung.*: Actovegin†; *India*: Placentrex; *Indon.*: Solcoseryl†; *Ital.*: Cellulin Retinale; Liposom; *Jpn*: Solcoseryl; *Malaysia*: Solcoseryl; *Mex.*: Aninegalem; Reposton†; *Philipp.*: Cerebrolysin; Solcoseryl; *Pol.*: Cerebrolysin; Solcoseryl; *Port.*: Cerebrolysine†; *Rus.*: Actovegin (Актовегин); Cerebrolysin (Церебролизин); Cortexin (Кортексин); Laennec (Лаэннек); Prostacor (Простакор); Prostatilen (Простатилен); Retinalamin (Ретиналамин); Samprost (Сампрост); Sirepar (Сирепар)†; Solcoseryl (Солкосерил); Uroprost (Уропрост); Vitaprost (Витапрост); *Singapore*: Solcoseryl; *Switz.*: Solcoseryl; *Thai.*: Cerebrolysin; Hepavit; Sirepar†; Solcoseryl; *Ukr.*: Actovegin (Актовегин); Cerebrocurin (Цереброкурин); Cerebrolysin (Церебролизин); Ceregin (Церегин); Cortexin (Кортексин); Haematogen (Гематоген); Inflamafertin (Инфламафертин); Propes (Пропес); Retinalamin (Ретиналамин); Solcoseryl (Солкосерил); Vitaprost (Витапрост).

Multi-ingredient Preparations. *Arg.*: ITE-B12 Forte; Melagel; Pat-Chobet; Peptonum; Tricomax; *Austral.*: Hepasol; *Austria*: Aktivanad; Intestinol†; Solcoseryl Dental; Wobe-Mugos; *Braz.*: Dobiron; Extrato Hepatico Composto; Ferrocomplex; Fol Sang†; Hematiase B12; Lisotox; Panvitrop; Rubrargil; Xantinon B12; *Canad.*: Digestolax; Super Energex Plus†; *Chile*: Rumalon; Tonopron Puerte Con Vit. B12; *Ger.*: Aktivanad-N; Dia-Aktivanad-N; Enzym Comp; Enzym-Harongan; Enzynorm f; Factor AF2; FegaCoren; NeyDesib Nr 78; Solcoseryl akut†; Solcoseryl Dental†; *Hong Kong*: Portifer; Solcoseryl Dental; *Hung.*: Dipankrin; Neogranormon; *India*: Bayers Tonic; Deferon; Hepatoglobine; Iberol; Lederplex; Livogen; Mynberrys Compound; Neo-Hepatex; Plastules B-12; Surbex T; *Indon.*: Bioplacenton; Centabio; Cyltabs; LaktaFit; Milmor; Moloco + B12; Neocenta; Solcoseryl Dental†; Tonikum Bode; Villron; *Irl.*: Perybar†; *Ital.*: Biotrefon Plus; Gastro-Pepsin; Vigogel; *Malaysia*: Solcoseryl Dental; *Mex.*: Cholal Modificado; *Philipp.*: Godex†; Godex; Mitodex; Solcoseryl Dental; *Port.*: Cognicer; *Rus.*: Cholenzim (Холензим); Erbisol (Эрбисол); Prohepar (Прогепар); Solcoseryl Dental (Солкосерил Дентальная); *S.Afr.*: Liviton; Prohep†; Zeel; Zeel; *Singapore*: Solcoseryl Dental; *Spain*: Hepadif; Policolinosil; *Switz.*: Solcoseryl Dentaire; Wala Echinacea; *Thai.*: Intricon; Solcoseryl Dental; Vitaral; *Turk.*: Solcoseryl; *UK*: Hematinic; S.P.H.P.; *Ukr.*: Hepadif (Гепадиф); Hepadif (Гепадиф); Solcoseryl Dental (Солкосерил Дентальная); *USA*: Albafort; Feocyte; FeoGen; Geritonic; I-L-X; Iron Complex; Multigen; Trimagen†; Vitagen Advance.

Homoeopathic Preparations. *Austral.*: Oscillococcinum; *Austria*: Berberis Cosmoplex†; *Canad.*: Complete Flu Care 4 Kids†; Fibromyalgie; Homeocoksinum; Hylands Flu; Hylands Formula F; Oscillococcinum; *Cz.*: Dolicoccil†; Stodal; Zeel Salbe†; *Fr.*: Enterokinasum Compose; Hepatodrainol; Hypophysis Complexe No 31†; Oscillococcinum; *Ger.*: AntiFocal Nr 69-Sol L†; Conisan A†; Conisan B†; Conjunctisan-AN†; Conjunctisan-BN†; Crataegus comp; EK Burger†; Glandulae-F-Gastreu R20; Hepar comp; Hepar-Magnesium; Hepar-Stannum†; Hewelymphon N†; Infihepan; Mucosa compositum; Ney Opin Nr 58; NeyArthros Nr 43-Sol†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyAthos Nr 43; NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; NeyDIL Nr 70; Neydin-P†; Neydin-M†; NeyDop Nr 97; Ney-Faexan Nr 55; NeyFegan Nr 26; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyIm Nr 73 pro injectione; NeyImmun Nr 73-Sol†; NeyLing Nr 66; Ney-Normin Nr 65; NeyPson Nr 5; NeySol L 66†; NeyTroph Nr 96 oral†; NeyTroph Nr 96 pro injectione; NeyTroph Nr96-Sol†; Sanochond; *Hung.*: Dolicoccil; Oscillococcinum; Zeel; *Neth.*: Chavita 6; Emvita 10; Emvita 11; Emvita 26; Geovita; Hepatodrainol†; Neurovita; Oscillococcinum; Urtizon complex; *Port.*: Hepatodrainol; Oscillococcinum; *Rus.*: Oscillococcinum (Осциллококцинум); Zeel T (Цель Т); *Switz.*: Fluzinum; Influostim; Oscillococcinum; *Ukr.*: Oscillococcinum (Осциллококцинум); Stodal (Стодаль).

Aniseed

Anice; Anis; Anis, fruit d'; Anís, semilla de; Anis Verde; Anis Vert; Anise; Anise Fruit; Anise Seed; Anisi fructus; Ánizstermés (fruit); Anyžių vaisiai (fruit); Anýzový plod (fruit); Owoc anyżu (fruit); Анис.

UNII — 21C2F5E8RE.

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

Ph. Eur. 8: (Aniseed; Anisi Fructus). The whole dried fruit of *Pimpinella anisum*, containing not less than 2% v/w of essential oil calculated with reference to the anhydrous drug. It has an odour reminiscent of anethole. Protect from light.

Profile

Aniseed is carminative and mildly expectorant; it is used mainly as anise oil or as preparations of the oil. It may cause contact dermatitis, probably due to its anethole content.

Aniseed is the source of anise oil (below).

References.

1. Chandler RF, Hawkes D. Aniseed—a spice, a flavor, a drug. *Can Pharm J* 1984; 117: 28–9.
2. Praj J, *et al.* Occupational asthma induced by aniseed. *Allergy* 1996; 51: 337–9.
3. Garcia-Gonzalez JJ, *et al.* Occupational rhinoconjunctivitis and food allergy because of aniseed sensitization. *Ann Allergy Asthma Immunol* 2002; 88: 518–22.
4. Gázquez García V, *et al.* Aniseed-induced nocturnal tongue angioedema. *J Investig Allergol Clin Immunol* 2007; 17: 406–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Wunderbalsam; *Austral.*: Colon Care; Detox Program; HRF; Neo-Cleanse; *Austria*: Asthmatee EF-EM-ES; Brady's-Magentropfen; Euka; Hustensaft Weleda; *Braz.*: Balsamo Branco; Camomila; *Canad.*: Digestol; Floradix Kindervital†; Formula T4†; Herbal Laxative†; *Chile*: Paltomiel; *Fr.*: Elixir Bonjean†; Herbesan; Mucinum a l'Extrait de Cascara; Tisane Provencale no 5†; *Ger.*: Floradix Multipretten N; Weleda Hustenelixier; *Hung.*: Herbalakt; Salus Multipretten; *Israel*: Jungborn†; *Ital.*: Cadifen; Cadimint; Dicalmi; Tisana Kelemata; *Neth.*: Verzachtende Hoestsiroop met tijm; *Pol.*: Apinorm†; Syrop Sosnowy Zlozony; *Port.*: Mucinum; *Rus.*: Kliophyt (Клиофит); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Pectorales Species No 3 (Грудной Сбор 3); *S.Afr.*: Clairo†; Cough Elixir†; Pragador†; *Spain*: Crislaxo; Laxante Sanatorium†; *Swed.*: Alpenkraft; Multipretten; *Switz.*: Elixir contre la toux†; Kernosan Elixir; Kernosan Heidelberger Poudre; Metabol; Tisane favorisant l'allaitement; *Turk.*: Naneson; *UK*: Herb and Honey Cough Elixir; Revitonil; *Ukr.*: Liponorm (Липонорм); Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. *Canad.*: Voxpax†; *Fr.*: Voxpax; *UK*: Cough Elixir; Pragador; Laxadoron.

Anise Oil

Anís, aceite esencial de; Anis, huile essentielle d'; Aniseed Oil; Anisi Aetheroleum; Anisi Ætheroleum; Anisöl; Anisolja; Anisõljy; Ánizsolaj; Anyžių eterinis aliejus; Anýzová silice; Essencia de Anís; Essence d'Anis; Olejek anyżowy; Oleum Anisi; Анисовое Масло.

ATC Herb — HR05WA5032 (Pimpinella anisum: *essential oil*), *HA03AW5048* (Pimpinella anisum: *fruit*); *HR05WA5033* (Pimpinella anisum: *fruit*); *HA03AW5047* (Pimpinella anisum: *essential oil*).

UNII — 6Y89129C8H.

NOTE. The name anise oil is also applied to Star Anise Oil, p. 2622.2.

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

Ph. Eur. 8: (Anise Oil; Anisi Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Pimpinella anisum*. It contains less than 1.5% linalol, 0.5 to 5.0% estragole, less than 1.2% α-terpineol, 0.1 to 0.4% *cis*-anethole, 87 to 94% *trans*-anethole, 0.1 to 1.4% anisaldehyde, and 0.3 to 2.0% pseudoisoeugenyl 2-methylbutyrate. A clear, colourless or pale yellow liquid. Relative density 0.980 to 0.990. F.p. 15 degrees to 19 degrees. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15 degrees. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of anise oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; 210: 100.

Profile

Anise oil is carminative and mildly expectorant and is a common ingredient of cough preparations. It is also a flavour. Anise oil is used in aromatherapy.

It may cause contact dermatitis, probably due to its anethole content.

For references to aniseed and anise oil, see Aniseed, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Paranix; *Austral.*: Digestive Aid; Gartech†; Moov Head Lice Shampoo; *Austria*: Bradosol; Bronchostop; Heumann's Bronchialtee; Kamillosan; Luuf-Hustentee; Neo-Angin; *Canad.*: Anifen†; *Cz.*: Bronchosan†; Neo-Angin; Stopangin; Stopangin; *Fr.*: Aromadetox†; Aromadigest†; Paregorique†; *Ger.*: Bronchoforton†; Ephepect-Pastillen N; Floradix Multipretten N; Heumann Bronchialtee Solubiflx T; Kamillosan Mundspray†; Paranix; Pulmotin; Repha-Os†; Salviathymol N; Sinuforton†; Verdauungstropfen Gastrofunkten†; *Hong Kong*: Ephepect Blocker; *Hung.*: Carmol; Salus Multipretten; *India*: Bestozyme P; Bestozyme; Kamillosan-N; Merozyme-C; Neopeptine; *Indon.*: Bital; Minyak Telon Cap Tiga Anak†; OBH; Silex; Telon 3 Anak; *Neth.*: Bronchicum; *Philipp.*: Kamillosan M; *Pol.*: Carmolis; Herbolen D†; Tobacoff; *Rus.*: Bronchosan (Бронхосан); Carmolis (Кармолис); Carmolis

Fluid (Кармолис Жидкость); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mixture Conta Tussis for Children (Микстура От Кашля Для Детей); Pectorales Elixir (Грудной Эликсир); Stopangin (Стопангин); *S.Afr.*: Borsdruppels; Paragoriese-Elikser†; Puma Cough Balsam†; *Spain*: Carminativo Juventus; H Tussan†; *Switz.*: DemoPectol; Impuls pastilles pour les bronches; Kamillosan; Makaphyt Gouttes antitussives†; Odontal; Paranix; Pastilles bronchiques S; Pastilles pectorales du Dr. Welti; Penta†; Rotpunkt Apotheke pastilles pour les bronches avec codeine; *Thai.*: Corinap; Gas-Nep; Mesto-Of; Rheum; *Turk.*: Myo-Oil; *UK*: Hactos; Honey & Molasses; Lightning Cough Remedy; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Slippery Elm Stomach Tablets; Vegetable Cough Remover; Zubes Blackcurrant; Zubes; *Ukr.*: Bronchial Balsam Bells (Бронхиальный Бальзам Белис); Bronchosan (Бронхосан)†; Kofanol (Кофанол)†; Stopangin (Стопангин); Stopangin (Стопангин).

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Compound Orange Spirit; Concentrated Anise Water; Concentrated Camphorated Opium Tincture;

USNF 31: Compound Orange Spirit.

Anisodamine

6-Hydroxyhyoscyamine.

$C_{17}H_{23}NO_4$=305.4.

CAS — 55869-99-3.

UNII — 013J3Q8EL8.

Pharmacopoeias. *Chin.* has a monograph for Raceanisodamine and Anisodamine Hydrobromide.

Profile

Anisodamine is an alkaloid isolated from *Scopolia tangutica* (*Anisodus tanguticus*), a plant used as a traditional medicine in China. It is related to atropine and hyoscyamine and has similar antimuscarinic properties (p. 1310.3). Anisodamine is given orally for its spasmolytic actions in the treatment of gastrointestinal spasm. It has also been tried in circulatory disorders, septic shock, and organophosphorus poisoning.

References.

1. Poupko JM, *et al.* The pharmacological properties of anisodamine. *J Appl Toxicol* 2007; 27: 116–21.
2. Pu XH, *et al.* Effect of intracoronary administration of anisodamine on slow reflow phenomenon following primary percutaneous coronary intervention in patients with acute myocardial infarction. *Chin Med J (Engl)* 2007; 120: 1226–31.

Antimony

Antimoine; Antimon; Antimonio; Stibium; Сурьма.

Sb=121.76

CAS — 7440-36-0.

UNII — 9IT35J3UV3 (antimony); 069647RPT5 (antimony ion Sb^{3+}).

Antimony Arsenate

AsO_4Sb=260.7.

CAS — 28980-47-4.

UNII — WE3458XNFT.

Antimony Pentasulfide

Antimonial Saffron; Antimonium Sulfuratum Aureum; Antimony Red; Golden Antimony Sulfide.

Sb_2S_5=403.8.

CAS — 1315-04-4.

UNII — 1433F1186N.

Antimony Trisulfide

Antimonous Sulfide; Antimony Glance; Antimony Sulfide; Antimony Sulphide; Antimony Trisulfide Colloid (USAN); Antimony Trisulphide; Needle Antimony; Stibnite.

Sb_2S_3=339.8.

CAS — 1345-04-6.

UNII — F79059A38U.

Profile

Antimony is a semi-metal or metalloid. It exists in several oxidation states, of which the trivalent (3+) and pentavalent (5+) are most important. Antimony and its compounds (antimonials) have industrial uses and toxicity has been reported from occupational exposure. They have also been used medicinally, but less toxic compounds are usually preferred; trivalent antimony compounds (p. 151.2) have been used as anthelmintics while pentavalent antimony compounds (p. 926.3) are used in leishmaniasis.

Antimony trisulfide, as kohl, has been used in cosmetics. An antimony trisulfide colloid labelled with technetium-99m has been used in lymphoscintigraphy.

Homoeopathy

Antimony and its compounds, including the trisulfide, pentasulfide, and arsenate have been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Hamorrhoidal-Zapfchen.

Multi-ingredient Preparations. *S.Afr.*: Heilsalbe†; Stibium Comp†; Wecesin†; *Switz.*: Suppositoires contre les hemorroides; Wecesin.

Homoeopathic Preparations. *Austral.*: IBS Eze; *Austria*: Birkenkohle comp; Prostsalbe†; Gastricumeel; Globuli gegen Husten Nr 2; Lymphdiaral; *Canad.*: Adrisin†; Cold Sores & Fever Blisters; Formula ES 211; Formula Homeo QR 209†; Fucus L111†; Headache & Migraine; Homeo-Form MI†; Homeoknop Bioactiv O Weight Loss Aid†; Hylavir FB†; Ind Complex†; War Complex†; *Chile*: Bioactiv O; Lessfat; *Fr.*: Abbe Chaupitre no 10†; Cina Compose; Fucus Complexe No 111; Ipeca Compose; Silicea Complexe No 11; Silmum†; Soreal; Verrulia; *Ger.*: Birkenkohle comp; Broncho-Injektopas; Bronchopas; Gastritis Complex; Hautfunktionstabletten N; Hautfunktionstropfen N; Infifer N; Lymphdiaral sensitive N; Lymphdiaral; Nuxal comp; Nuxal H; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Rufebran broncho†; Sinupas; Tussistin S; Wecesin; Weleda Heilsalbe; *Neth.*: Apo-STOM; Cutis comp; Gastricumeel; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Lymphdiaral; Phonix Hydrargyrum; Phonix Solidago comp; Tussistin; *S.Afr.*: Achillea Comp†; Hamamelis Comp†; *Switz.*: Gastricumeel; *UK*: Balsamicum; Frost Cream; WCS Dusting Powder.

Apis Mellifera

Abeille domestique; Abeja de la Miel; The honey bee; Медоносная Пчела Домашняя.

UNII — 7S82P3R43Z (Apis mellifera); *76013O881M* (Apis mellifera venom).

Pharmacopoeias. *Eur.* (see p. vii) includes the live worker honey bee for homoeopathic preparations.

Ph. Eur. 8: (Honey Bee for Homoeopathic Preparations; Apis Mellifera ad Praeparationes Homoeopathicas). Live worker honey bee, *Apis mellifera*.

Profile

The honey bee, *Apis mellifera*, is a source of purified honey (p. 2072.1), royal jelly (p. 2608.1), propolis (p. 2597.3), beeswax (p. 2170.2) and bee pollen (see Pollen and Pollen Extracts, p. 2593.3).

Homoeopathy

Preparations of *Apis mellifera* have been used in homoeopathic medicines under the following names: Apis; Apis mellifica; Apis mel; Apis mell.

Allergen immunotherapy. For reference to the use of whole body extracts or venom from Hymenoptera spp. for allergen immunotherapy in allergic subjects, see p. 2435.1.

Arthritis. Bee venom has traditionally been used in the treatment of arthritis.[1,2] Studies *in vitro* have shown that bee venom has anti-inflammatory activity similar to that of cyclophosphamide. Melittin appears to be the active constituent, and seems to act by interfering with superoxide radical production from human leucocytes.[1]

1. Somerfield SD. Bee venom and arthritis: magic, myth or medicine? *N Z Med J* 1986; 99: 281–3.
2. Caldwell JR. Venoms, copper and zinc in the treatment of arthritis. *Rheum Dis Clin North Am* 1999, 25: 919–28.

Hypersensitivity. There were 14 reports of suspected adverse effects (10 considered serious), including allergic reactions, involving bee products such as bee pollen (p. 2593.3), propolis (p. 2597.3), and royal jelly (p. 2608.1) reported to the Canadian health authorities (Health Canada) between January 1998 and October 2004.[1]

There have also been reports of allergic contact dermatitis to propolis identified through patch testing,[2,3] and a case of occupational contact dermatitis.[4]

Anaphylactoid reactions[5] and acute severe exacerbations of asthma[6-9] (one fatal[7]) have occurred in atopic individuals who took royal jelly.

Hypersensitivity reactions to topical beeswax (p. 2170.2) products have been reported rarely. Contact dermatitis from use of a beeswax-based nipple protector has been reported,[10] and cheilitis from beeswax lip products has also occurred.[11] In some,[10,12] but not all,[11] cases, sensitivity may be related to propolis content in beeswax.

1. Health Canada. Products derived from bees: serious adverse reactions. *Can Adverse React News* 2005; 15 (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2eng.pdf (accessed 08/08/08)
2. Giusti F, *et al.* Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis* 2004; 51: 255–8.
3. Walgrave SE, *et al.* Allergic contact dermatitis from propolis. *Dermatitis* 2005; 16: 209–15.
4. Lieberman HD, *et al.* Allergic contact dermatitis to propolis in a violin maker. *J Am Acad Dermatol* 2002; 46 (suppl): S30–S31.
5. Takahama H, Shimazu T. Food-induced anaphylaxis caused by ingestion of royal jelly. *J Dermatol* 2006; 33: 424–6.
6. Thien FCK, *et al.* Royal jelly-induced asthma. *Med J Aust* 1993; 159: 639.
7. Bullock RJ, *et al.* Fatal royal jelly-induced asthma. *Med J Aust* 1994; 160: 44.
8. Peacock S, *et al.* Respiratory distress and royal jelly. *BMJ* 1995; 311: 1472.
9. Thien FCK, *et al.* Asthma and anaphylaxis induced by royal jelly. *Clin Exp Allergy* 1996; 26: 216–22.
10. García M, *et al.* Allergic contact dermatitis from a beeswax nipple-protective. *Contact Dermatitis* 1995; 33: 440–1.
11. Lucente F, *et al.* Contact cheilitis due to beeswax. *Contact Dermatitis* 1996; 35: 258.
12. Jacob SE, *et al.* Allergic contact dermatitis to propolis and carnauba wax from lip balm and chewable vitamins in a child. *Contact Dermatitis* 2008; 58: 242–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Joint & Muscle Cream; *Canad.*: Libeeda for Men; *Cz.*: Apisarthron†; *Hung.*: Apisarthron; Melliora; Rheudol; *Rus.*: Apisarthron (Апизартрон); *S. Afr.*: Bolus Eucalypti Comp†; *Ukr.*: Apisarthron (Апизартрон).

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Joint & Muscle Oral Spray†; Respatona Sore Throat; Snore Eze; Sports Ice Joint & Muscle; *Austria*: Apozema Allium Cepa compositum; Apozema Apis compositum; Bolus Eucalypti Comp; Erbiode Allergie; Erysidoron Nr 1; Globuli gegen Halsweh Nr 2; Globuli gegen Heiserkeit; Iris Med Complex; *Canad.*: Angeel†; Arnica-Heel Comp†; Arthritic Pain; Cruroheel S†; EnurAid; Erysidoron 1†; Execalm†; Hay Fever; Hives; Homeo-Form AR†; Hylands Formula E; Larydol†; Lympatox; Pollen Plus; Renelix; SK Complex†; *Chile*: Apis Compuesto; *Cz.*: Angin-Heel S; Galium; *Fr.*: Aconitum Compose†; Agnus Castus Complexe No 2†; Angipax; Boripharm No 10†; Dermo-Drainol†; Euphrasia Complexe No 115; Mercurius Cyanatus Complexe No 43†; Natrum Carbonicum Complexe No 10†; *Ger.*: Allergo-Loges; Angi Truw N; Angina-Gastreu S R1; Arnica comp/Apis†; Arthriplex; Arthrokatt; Dermi-cyl L Ho-Len-Complex; Desarell; Erysidoron 1; Febro-cyl L Ho-Len-Complex; Flenin; Genu-cyl L Ho-Len-Complex; HanoToxin M; Hanotoxin M; Hevertotox; Hewallergia Complex; Infekt-Komplex L Ho-Pu-Complex; Influex; Lowe-Komplex Nr 13; Lowe-Komplex Nr 5 Echinacea; Ossidal; Pascodem; Pascorenal N; Pascorenal-Injektopas; Pulmosan Infekt; Regasinum antallergicum; Sinusitis Hevert SL; Solidago Hevert Complex; Solidagosan N; toxi-loges; Toxiselect; Zahnungstropfen Escatitona; *Hung.*: Angin-Heel; *Neth.*: Akutur spag; Arnilite; Belachin-Gastreu R1; Echilite; Emvita 15; Emvita 20; Emvita 3; Emvita 4; Gynaelite; Homeocare keelspray; Lergilite; Prurilite; Urtizon complex; Vinceel H; *Rus.*: Climaxan (Климаксан); Dysmenorm (Дисменорм); Ruta-Plus (Рута-Плюс); Urtica-Plus (Уртика-Плюс); *S.Afr.*: Berberis/Cantharis Comp†; Erysidoron 1†; *Switz.*: Akutur; HerbAllerg; Regenaplex Nr 28a; Regenaplex Nr. 50b; *UK*: Bolus Eucalypti Comp; Erysidoron 1; *Ukr.*: Dysmenorm (Дисменорм.); Incena (Инцена); *USA*: Preferred Remedies Allergy.

Apricot

Абрикос.

UNII — 10TCS27K2T (Prunus armeniaca); *269CJD5GZ9* (Prunus armeniaca fruit); *YX387ZG375* (Prunus armeniaca juice); *0X5YG5R83N* (Prunus armeniaca leaf); *75356789W* (Prunus armeniaca seed).

Pharmacopoeias. *Chin.* includes Bitter Apricot Seed, the kernel obtained from various species of *Prunus*. *Jpn* includes a monograph for Apricot Kernel.

Profile

The kernels of the apricot, *Prunus armeniaca* (*Armeniaca vulgaris*; *P. tiliifolia*) (Rosaceae), are used in Chinese medicine for disorders of the respiratory tract and for constipation.

Apricot is a source of persic oil (p. 2587.1). Amygdalin, the major cyanogenic glycoside of apricot kernels, is the major constituent of laetrile (p. 2539.3). Apricot kernels are also a source of pangamic acid (p. 2582.1).

Apricot fruits are used as a food.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Jpn*: Colgen Maoto; Gokoto; Junchoto; Makyokanseikito; Makyoyokukanto; Maoto; Mashiningan; Ryokankyomishingeninto; Seihaito; Shimpito; *Singapore*: New Tonin Troche; *Ukr.*: Ventero-Nova (Вентеро-Нова).

Aptiganel *(pINN)*

Aptiganelum; Аптиганел.

1-(*m*-Ethylphenyl)-1-methyl-3-(1-naphthyl)guanidine.

$C_{20}H_{21}N_3$=303.4.

CAS — 137159-92-3.
UNII — 46475LV84I.

Aptiganel Hydrochloride *(USAN)*

CNS-1102.
$C_{20}H_{21}N_3.HCl$=339.9
CAS — 137160-11-3.
UNII — 40PWH14OXW.

NOTE. The name Cerestat has been used as a trade mark for aptiganel hydrochloride.

Profile

Aptiganel is a guanidine derivative that antagonises the effects of the excitatory amino-acid neurotransmitter glutamate at NMDA-receptors. It has been given intravenously in the investigation of the prevention of ischaemic brain damage in patients with traumatic head injury or stroke.

After dose-ranging studies of aptiganel in healthy subjects[1] and in patients,[2] adverse effects reported[3] in patients with acute ischaemic stroke, at doses that had been neuroprotective in *animals*, included an increase in systolic blood pressure and an excess of CNS effects. A randomised controlled study[4] in patients with acute ischaemic stroke was suspended because of a lack of efficacy and a potential imbalance in mortality compared with placebo.

1. Muir KW, *et al.* Pharmacological effects of the non-competitive NMDA antagonist CNS 1102 in normal volunteers. *Br J Clin Pharmacol* 1994; 38: 33–8.
2. Block GA, *et al.* Final results from a dose-escalating safety and tolerance study of the non-competitive NMDA antagonist CNS1102 in patients with acute cerebral ischaemia. *Strokr* 1995; 26: 185.
3. Dyker AG, *et al.* Safety and tolerability study of aptiganel hydrochloride in patients with an acute ischemic stroke. *Stroke* 1999; 30: 2038–42.
4. Albers GW, *et al.* Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. *JAMA* 2001; 286: 2673–82.

Arachidonic Acid

(all-*Z*)-Eicosatetraenoic Acid.
(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-Eicosatetraenoic acid.
$C_{20}H_{32}O_2$=304.5
CAS — 506-32-1 ((all-Z)-eicosatetraenoic acid); 7771-44-0 (eicosatetraenoic acid).
UNII — 27YG812J1I.

Profile

Arachidonic acid is an omega-6 polyunsaturated fatty acid and is an important component of mammalian cell membranes; it acts as a precursor for the production of some eicosanoids such as prostaglandins (see p. 2598.1). Arachidonic acid is an essential fatty acid and has been used in nutritional supplements for infants. Its role as a supplement in adults is controversial.

References.

1. Calder PC. Dietary arachidonic acid: harmful, harmless or helpful? *Br J Nutr* 2007; 98: 451–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Cycloferon (Циклоферон); *Ukr.*: Cycloferon (Циклоферон).

Multi-ingredient Preparations. *Indon.*: Biolysin Smart; Brainvit; Cerebrofort AA+DHA; Cerebrofort Gold; Curfos; Curvit CL; Folamil Genio; Lysmin Plus; Mulsanol; Natavit; Prokids; *NZ*: Efanatal; *Singapore*: Dhaxtra; Mumomega Equazen†; Nata-Boost; Natal Care.

Arachis Oil

Aceite de maní; Arachide, huile d', raffinée; Arachidis Oleum; Arachidis Oleum Raffinatum; Cacahuete, aceite de; Earth-nut Oil; Erdnussöl; Finomított földimogyoróolaj; Ground-nut Oil; Huile d'Arachide; Jordnötolja, raffinerad; Maapähkinäöljy, puhdistettu; Nut Oil; Ol. Arach.; Olej arachidowy oczyszczony; Óleo de Amendoim; Oleum Arachis; Peanut Oil; Podzemnicový olej čištěný; Refined Arachis Oil; Žemės riešutų aliejus; Yerfıstığı Yağı; Масло Земляного Ореха; Арахисовое Масло.
ATC: Herb. — H05BA5001 (Arachis hypogaea: oil); H02WB5001 (Arachis hypogaea: oil).
UNII — 5TL50QU0W4.

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

Eur. also includes hydrogenated arachis oil.

Ph. Eur. 8: (Arachis Oil, Refined; Arachis Oil BP 2014). The refined fatty oil obtained from the shelled seeds of *Arachis hypogaea*. A suitable antoxidant may be added. It is a clear, yellowish viscous liquid consisting of glycerides, chiefly of oleic and linoleic acids, with smaller amounts of other acids. It solidifies at about 2 degrees. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

The BP 2014 gives Ground-nut Oil and Peanut Oil as approved synonyms.

Ph. Eur. 8: (Arachis Oil, Hydrogenated; Arachidis Oleum Hydrogenatum). Arachis oil that has been refined, bleached, hydrogenated, and deodorised. It is a white or faintly yellowish soft mass that melts to a clear pale yellow liquid when heated. Practically insoluble in water; very slightly soluble in alcohol; freely soluble in dichloromethane and in petroleum spirit (b.p. 65 degrees to 70 degrees). Protect from light.

USNF 31: (Peanut Oil). The fully-refined (alkali-refined, bleached, and deodorised at 230 degrees to 260 degrees) oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* (Leguminosae). It is a colourless or pale yellow, oily liquid with a bland taste; it may have a characteristic nutty odour. Very slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Profile

Emulsions containing arachis oil are used in nutrition. Arachis oil is given as an enema for softening impacted faeces. It is used in drops for softening ear wax (see under Docusates, p. 1836.3) and in emollient creams. Arachis oil is given orally, usually with sorbitol, as a gallbladder evacuant before cholecystography.

Precautions. It has been suggested that the use during infancy of preparations containing arachis oil, including infant formulas and topical preparations, may be responsible for sensitisation to peanut, with a subsequent risk of hypersensitivity reactions.[1-3] The arachis oil used in such preparations is refined oil and it has been pointed out that such oil should not contain the proteins that produce allergic reactions in susceptible people.[4,5] In the USA, heating of arachis oil during preparation, to further reduce protein content, has been proposed.[6] Nonetheless, some consider that sufficient protein may be present in refined oil to cause sensitisation.[7] However, others have pointed out that to date, there are no reliable data about doses of topical arachis oil needed to induce sensitisation via the epidermal route and that the benefit of protecting skin barrier functions in atopic patients with products using refined arachis oil outweigh possible risks of sensitisation.[8] In the UK, the CSM considered that there was not enough evidence to conclude that medicinal products containing arachis oil could lead to sensitisation.[9] However, although they considered the risk of a reaction to be low, they recommended that patients known to be allergic to peanuts should not use medicines containing arachis oil (nor, because of the possibility of cross-sensitivity, should patients allergic to soya), and that such medicines should include an appropriate warning in the labelling.

1. de Montis G, *et al.* Sensitisation to peanut and vitamin D oily preparations. *Lancet* 1993; 341: 1411.
2. Lever LR. Peanut and nut allergy: creams and ointments containing peanut oil may lead to sensitisation. *BMJ* 1996; 313: 299.
3. Lack G, *et al.* Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; 348: 977–85.
4. Hourihane J O'B, *et al.* Randomised, double blind, crossover challenge study of allergenicity of peanut oil in subjects allergic to peanuts. *BMJ* 1997; 314: 1084–8.
5. Committee on Toxicity of chemicals in Food, Consumer Products and the Environment. *Peanut allergy*. London: DoH, 1998.
6. Wilkin JK, *et al.* Peanut allergy. *N Engl J Med* 2003; 349: 302.
7. Lack G, *et al.* Peanut allergy. *N Engl J Med* 2003; 349: 302–3.
8. Ring J, Möhrenschlager M. Allergy to peanut oil — clinically relevant? *J Eur Acad Dermatol Venereol* 2007; 21: 452–3.
9. CSM/MHRA. Medicines containing peanut (arachis) oil. *Current Problems* 2003; 29: 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Oilatum†; *Denm.*: Olie†; *Fin.*: Calogen; *Ger.*: Olbad Cordes P†; *Indon.*: Oilatum Cream†; *Irl.*: Fletcher's Arachis Oil†; *Ital.*: Calogen; *Mex.*: Dermo Bell; Nutrisil; Oilatum; *NZ*: Calogen; *S.Afr.*: Oilatum Cream†; *UK*: Calogen.

Multi-ingredient Preparations. *Austral.*: Cerumol; *Austria*: Balneum P; *Cz.*: Balneum Hermal P; *Ger.*: Balneum P; *Hung.*: Balneum Hermal P; *India*: Oilade Bath; *Irl.*: Cerumol; Earex†; Polytar Emollient; Polytar; *Israel*: Balneum P; Cerumol; *Ital.*: Balneum Hermal Forte; *Pol.*: Balneum Hermal P†; *S.Afr.*: Cerumol; Haarlemensis; *Singapore*: Cerumol; Earex; *Spain*: Emolytar†; *Switz.*: Balmed Hermal P; *UK*: Cerumol; Earex; Hewletts†; Nowax; Red Oil; Soothol; *Venez.*: Nutricap.

Pharmacopoeial Preparations
BP 2014: Arachis Oil Enema.

Areca

Areca Nuts; Arecae Semen; Arekasame; Betel; Betel Nuts; Noix d'Arec; Nuez de areca; Nuez de betel; Areka.
UNII — 483O0360NZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of areca:

Daka; Gua; Maag; Mak; Marg; Pan parag; Pinang; Pugua; Puwak; Supai; Suparim.

Pharmacopoeias. In *Chin.* and *Jpn.*

Uses and Administration

Areca consists of the dried ripe seeds of *Areca catechu* (Palmae) containing the alkaloid arecoline.

Areca is used in Asian countries as a masticatory. It has sialogogue properties and is chewed for its mild intoxicant and euphoriant effects. The usual custom is to chew piece of areca seed (areca nut; betel nut) wrapped with lime (calcium hydroxide) in the leaf of the betel pepper (betelvine) (*Piper betle*, which is unrelated to areca). This preparation is known as 'betel quid' (betel) or 'paan' (pan masala), and produces a red juice when chewed, which stains the saliva, teeth and mucosa. Other ingredients that might be added include catechu gum, spices, or tobacco.

Areca was formerly used in the treatment of tapeworm infection, and arecoline has been used in veterinary medicine as a purgative and taenifuge.

Adverse Effects

Arecoline and arecaidine (produced by the hydrolysis of arecoline when chewed with lime—see Uses and Administration, above) have cholinergic activity, and adverse effects that may occur with initial or heavy use of areca include excessive salivation, sweating, lachrymation, urinary incontinence, or diarrhoea. An increased incidence of oral submucosal fibrosis, oral leucoplakia, and oral squamous cell carcinoma has been reported following habitual use.

Areca chewing. Discussions of the health risks associated with the chewing of preparations containing areca nut by indigenous populations in Asia[1-3] and immigrant groups in the UK,[4] USA,[5] and New Zealand,[6] including acute effects.[2,3,5] See also Adverse Effects of Tobacco Products under Nicotine (p. 2571.2) for reference to mixtures of areca and tobacco.

1. Mack TM. The new pan-Asian paan problem. *Lancet* 2001; 357: 1638–9.
2. Deng JF, *et al.* Acute toxicities of betel nut: rare but probably overlooked events. *J Toxicol Clin Toxicol* 2001; 39: 355–60.
3. Chu NS. Effects of betel chewing on the central and autonomic nervous systems. *J Biomed Sci* 2001; 8: 229–36.
4. Warnakulasuriya S, *et al.* Areca nut use: an independent risk factor for oral cancer. *BMJ* 2002; 324: 799–800.
5. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; 34: 238–43.
6. Yoganathan P. Betel chewing creeps into the New World. *N Z Dent J* 2002; 98: 40–5.

Carcinogenicity. Precancerous and cancerous conditions of the oral cavity have been attributed to the chewing of preparations containing areca (see Uses and Administration, above). In betel-chewer's mucosa, the oral mucosa is discoloured and there is desquamation or peeling of the oral epithelium from the traumatic effect of chewing and possibly a chemical action of the constituents. This condition may be a precursor of oral submucosal fibrosis, which is considered to be precancerous.[1] Oral leucoplakia is another precancerous condition that is reported. The role of areca in the development of these conditions and oral squamous cell carcinoma has been debated. The effects may be due to the arecaidine content of areca, the alkalinity of the lime, presence of tobacco, or a combination of these.[2,3] Results from a case-controlled study[4] point to an independent association between oral squamous cell carcinoma and chewing areca seeds in preparations without tobacco compared with non-users of areca. A review[5] of available evidence strongly supports this association.

1. Reichart PA, Phillipsen HP. Betel chewer's mucosa—a review. *J Oral Pathol Med* 1998; 27: 239–42.
2. Norton SA. Betel: consumption and consequences. *J Am Acad Dermatol* 1998; 38: 81–8.
3. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; 34: 238–43.
4. Merchant A, *et al.* Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer* 2000; 86: 128–31.
5. Nair U, *et al.* Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. *Mutagenesis* 2004; 19: 251–62.

Effects on the lungs. Evidence suggesting that there is an association between betel-nut chewing and bronchoconstriction in asthmatic patients.[1,2]

1. Taylor RFH, *et al.* Betel-nut chewing and asthma. *Lancet* 1992; 339: 1134–6.
2. Kiyingi KS. Betel nut chewing and asthma. *Lancet* 1992; 340: 59–60.

Effects on the nervous system. Areca-nut (betel-nut) chewing is associated with habituation, addiction, and dependence,[1] and CNS symptoms of withdrawal have been described in 2 patients.[2] A case of neonatal withdrawal syndrome in an infant born to a chronic areca-nut user has also been reported.[3] Psychosis has also been reported.[1]

It has been suggested that the muscarinic action of areca alkaloids may have a beneficial effect on symptoms of schizophrenia, and a study of such patients in a Micronesian population provides some support for this idea.[4] However, severe extrapyramidal symptoms followed betel-nut chewing in 2 patients with chronic schizophrenia who were also receiving antipsychotic therapy.[5]

1. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med* 1999; 34: 238–43.
2. Wiesner DM. Betel-nut withdrawal. *Med J Aust* 1987; 146: 453.
3. López-Vilchez MA, *et al.* Areca-nut abuse and neonatal withdrawal syndrome. Abstract: *Pediatrics* 2006; 117: 203. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/1/e129.pdf (accessed 16/08/10)
4. Sullivan RJ, *et al.* Effects of chewing betel nut (Areca catechu) on the symptoms of people with schizophrenia in Palau, Micronesia. *Br J Psychiatry* 2000; 177: 174–8.
5. Deahl MP. Psychostimulant properties of betel nuts. *BMJ* 1987; 294: 841.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Good Time; Herr; Himplasia; Lukol; *Jpn*: Nyoshinsan; *Ukr.*: Evica (Евика)†.

Aristolochia

Serpentaria

CAS — 313-67-7 (aristolochic acid).

NOTE. *Aristolochia clematitis* has also been known as asarabacca (p. 2449.3).

Pharmacopoeias. In *Chin.* as Herba Aristolochiae (Tianxianteng; Dutchman's Pipe Vine), which allows *Aristolochia debilis* or *A. contorta*.

Uses and Administration

Aristolochia spp. (birthworts) including *A. clematitis* and *A. labiata (A. brasiliensis)* have been used in herbal medicine. Chinese medicine has employed various species of *Aristolochia* including *A. contorta*, *A. debilis*, and *A. manshuriensis*. The terms Mu Tong and Fangji have been used for *Aristolochia* spp. in traditional medicine.

Serpentary (serpentaria) is the dried rhizome and roots of *Aristolochia serpentaria* (Virginian snakeroot) and of *A. reticulata* (Texan snakeroot) (Aristolochiaceae). However, snakeroot is also used as a common name to describe poisonous *Eupatorium* spp. Preparations of serpentary have been used as bitters.

The active ingredient is aristolochic acid, which has been tried in inflammatory disorders, mainly in folk medicine; the sodium salt of aristolochic acid has also been used. However, there is concern over the use of *Aristolochia* and aristolochic acid because of serious toxicity and preparations have been banned in some countries—see below

Adverse Effects

Chronic ingestion of aristolochic acid present in *Aristolochia* spp. has been associated with serious nephrotoxicity and carcinogenicity.

Effects on the kidneys. Progressive interstitial fibrosis of the kidney related to a slimming regimen containing Chinese herbs had been reported in 70 patients in Belgium by 1993; 30 of these patients had terminal renal failure.[1] Renal failure has also been reported[2] in 2 patients in the UK after ingestion of Chinese herbal medicines that were later found to contain aristolochic acid, a known nephrotoxin;[3] one of these patients subsequently developed invasive urothelial carcinoma.[4] Inadvertent ingestion of aristolochic acid can originate as a result of the substitution of *Aristolochia* spp. (probably *A. manshuriensis*) for other innocuous herbal substances;[2,5] the Belgian cases were probably as a result of substitution of *A. fangchi* extracts for *Stephania tetrandra*.[1] As a result of these cases, the UK MCA issued a permanent ban on *Aristolochia* preparations in 1999. Similar bans have been made in several other countries;[3] in 2004, the Chinese regulatory authority also banned the use of *A. fangchi* and *A. debilis* in traditional medicine formulations. Examination of 39 patients in Belgium with nephropathy associated with *A. fangchi* ingestion had revealed 18 cases of urothelial carcinoma and evidence of mild to moderate dysplasia in 19 patients.[6] There had appeared to be a higher risk of carcinoma with total doses of *A. fangchi* in excess of 200 g.

Aristolochic acid has been proposed as the cause of endemic (Balkan) nephropathy,[7] which is confined to a very specific rural geographical distribution and first described in the 1950s. Data supporting this hypothesis included findings of DNA damage linked to aristolochic acid in kidney samples from affected patients, as well as renal failure in horses who had grazed in the local fields. *Aristolochia clematitis* is endemic to the region and has been found in fields cultivated for wheat grain. It is possible that the local population could be exposed to toxic amounts of aristolochic acid over time from bread made with grain contaminated with *A. clematitis* seeds.

1. Vanhaelen M, *et al.* Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; 343: 174.
2. Lord GM, *et al.* Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; 354: 481–2.
3. Cosyns JP. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. *Drug Safety* 2003; 26: 33–48.
4. Lord GM, *et al.* Urothelial malignant disease and Chinese herbal nephropathy. *Lancet* 2001; 358: 1515–6.
5. But PP, Ma S-c. Chinese-herb nephropathy. *Lancet* 1999; 354: 1731–2.
6. Nortier JL, *et al.* Urothelial carcinoma associated with the use of a chinese herb (Aristolochia fangchi). *N Engl J Med* 2000; 342: 1686–92.
7. Grollman AP, *et al.* Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 2007; 104: 12129–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Euserpina Cellulite.

Multi-ingredient Preparations. *S.Afr.*: Borstol Cough Remedy†.

Homoeopathic Preparations. *Canad.*: Detox L37; *Switz.*: Menstruasan.

Arjuna

Arjun; Arjun Myrobalan.

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — Arjuna, above; *T. bellirica* — see Beleric Myrobalan, p. 2453.2; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Arjuna Stem Bark). The cut dried bark of the stems of *Terminalia arjuna*. It contains not less than 6% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The bark of arjuna, *Terminalia arjuna* (Combretaceae), is used in Ayurvedic medicine mainly for cardiovascular disorders. It is also included in herbal preparations for liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Herbadict; *Pol.*: Liv 52; *Rus.*: Liv 52 (Лив 52); Liv 52 (Лив 52); *Singapore*: Liv 52; Liv 52; *Switz.*: Liv 52; *Ukr.*: Bon-Apetit (Бон-Аппетит); Liv 52 (Лив 52); Trypsidan (Трипсидан)†.

Arnica

Arnica; Arnica, fleur d' (arnica flower); Arnicae Anthodium; Arnicae flos (arnica flower); Arniku žiedai (arnica flower); Arnikablomma (arnica flower); Arnikinkukka (arnica flower); Arnikový květ (arnica flower); Hegyi árnika virág (arnica flower); Koszyczek arniki (arnica flower); Leopard's Bane; Mountain Tobacco; Wolf's Bane; Wolfsbane; Арника.

ATC Herb — HD03WX5003 (Arnica montana *flower*).

UNII — QZ0E5Y15PZ (Arnica montana *flower*); *O80TY208ZW* (Arnica montana); *MUE8Y11327* (Arnica montana *root*).

NOTE. Wolfsbane is also used as a common name for aconite (p. 2428.3).

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

Ph. Eur. 8: (Arnica Flower; Arnica Flos). It consists of the whole or partially broken, dried flowerheads of *Arnica montana*. It contains not less than 0.4% w/w of total sesquiterpene lactones expressed as dihydrohelenalin tiglate, calculated with reference to the dried drug. It has an aromatic odour. Protect from light.

Profile

Arnica is generally used in the form of the flowerheads of *Arnica montana* (Compositae).

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Tincture of arnica may cause dermatitis when applied to the skin of sensitive persons.

Preparations of arnica flower and arnica root are used as astringents for topical application to unbroken skin in conditions such as sprains and bruises; such preparations are not considered suitable for internal use. Arnica flowers are the source of arnica oil, which has been used similarly.

Herbal preparations containing arnica are available for oral use.

Brazilian arnica (*Solidago chilensis*, arnica do campo) has been used for external application similarly to arnica.

Homoeopathy

Arnica has been used in homoeopathic medicines under the following names: Arnica montana; Arnica, Flos; Arnica montana e flore; Arnica montana ex herba; Arnica, Planta tota; Arnica montana ex planta tota; Arnica montana, radix; Arnica, rad; Arn. mont. Some homoeopathic preparations are available for oral use.

References.

1. Leivers K. Unravelling the confusion around arnica's herbal and homoeopathic use. *Pharm J* 2005; 275: 289–91.
2. Kouzi SA, Nuzum DS. Arnica for bruising and swelling. *Am J Health-Syst Pharm* 2007; 64: 2434–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Sports Ice Bruising Relief; *Belg.*: Arnican; *Chile*: Arnikaderm; *China*: Haojishi (Cool) (好及速 (冷感)); *Fr.*: Arnicagel; Arnican; Arnigel; Pharmadose teinture d'arnica; *Ger.*: Arnikatinktur; Arthrosenex N; Doc; *Irl.*: Arrogel; *Mex.*: Balsamo Nordin; Estimul; *Port.*: Arnigel; *Singapore*: SinEccH; *Spain*: ArnicaMed; *Switz.*: A Vogel Gel en cas de rhumatisme; AtroMed; *UK*: Arnicare; Arrogel; Bumps & Bruises.

Multi-ingredient Preparations. *Arg.*: CVP Cellulite; Fluido Spineda; Lavandula Oligoplex; *Austral.*: Accelerex painEASE; Accelerex painEASE; Hernidise; Joint & Muscle Cream; Percutane†; *Austria*: Arnicet†; Asthmatee EF-EM-ES; Berggeist; Cional; Dynexan; Heparin Comp; Rheuma; *Belg.*: Algi-Cool†; Purigel Crisp†; Purigel NP; *Canad.*: Arnica Ointment†; *Chile*: K-Gel; Lefkaflam; Matikomp; *Cz.*: Arnidol; *Fr.*: Arnicadol†; Decramp; Decramp; Dolores; Evarose†; Rap Phyto; Tigre de Chine; *Ger.*: Combudoron; Dolo-cyl†; Gothaplast Rheumamed AC†; Kneipp Arnika Salbe S; Retterspitz Ausserlich; Retterspitz Quick Muskel; Sportino Akut†; Trauma-cyl†; Varicylum-S†; Weleda Hauttonikum†; *Hong Kong*: New Patecs A†; *Hung.*: Forte Hirudo; Kobralgin; Kovitox; Medhirud; Melliora; Rheudol; *Irl.*: Combudoron†; Massage Balm with Arnica; *Ital.*: Clebolider†; Criotonal; Flebolider; Flodolor; Lactacyd Lentivo; Proctocella Complex; Vaginol; Vasotonal; Venalta; Venoplant; Wasotonal†; *Malaysia*: A-Bruzzy; Arnica Comp; *Mex.*: Arnident; Norex; Reudol; *Neth.*: Bioforce; *Pol.*: Arcalen; Arnisol; Dentosept A; Dentosept; Emorect; Escalar; Prostapol; Reumobonisol; Stomatosol; Uroprost; Venoforton; *Rus.*: Stomatophit (Стоматофит); *S. Afr.*: Arnica Massage Oil; Combudoron†; Dynexan; Lotio Pruni Comp cum Cupro†; Muscle Rub†; Wecesin†; Zeel; *Singapore*: A-Bruzzy; Scar Esthetique; *Switz.*: Combudoron; DUL-X Cool; DUL-X warm; DUL-X; Eucera avec camomille et arnica; Fortacet†; Gel de consoude†; Mucosan†; Onguent aux herbes Keller; Perskindol Cool Arnica; Topaceta†; Venadoron; Wecesin; *Turk.*: Symphosan; *UK*: Arnica Massage Balm; Hansaplast Herbal Heat Plaster; Profelan; *Ukr.*: Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит A); *USA*: Zim's Max Freeze; *Venez.*: Andantol Jalea; Gelsem.

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Echine†; Sports Ice Joint & Muscle; *Austria*: Arnica Komplex†; Arnica Med Complex; Aurumheel; Frostsalbe†; Ledum Med Complex; Memoria; Pumpan; Remasan; Repisan; Rheuma; Rhus Med Complex; Secale Med Complex; Thuja Med Complex; Traumeel; Tropfen bei Verletzungen; Zom; *Canad.*: Aches & Pains; Adrisin†; Angeel†; Arnica + Pain Relief; Arnica Cream†; Arnica-Heel Comp†; Arnicaid; Art Complex†; Arthritic Pain; Arthritis Pain Formula; Artis-Heel†; Ateria-Heel†; Aurumheel†; Backache with Arnica†; Barijodeel†; Bioactiv E†; Bioactiv R†; Bumps and Bruises; Calnor†; Capsicum + Arthri-Cream; Comp-Drops 94†; Drosera Complex; Drosera Plex†; Echinacea Compositum; Echinacea L40†; EnurAid; Fibromyalgie; Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; Homeo-Form AR†; Homeo-S-Asp; Hylagesic APF; Hylands Formula E; Hylands Leg Cramps; Ikoplex 12†; Ivernax; Jet Lag; Kids Cough & Cold Phytux; Kids' Teething; L52 Cough & Cold; Lympatox; Osteel†; Phytorux H; Roxalia; Soludor†; Sportenine; Traumeel; Zeel Comp; *Chile*: Anacardio con Fosforo; Arnica Compuesta; Arnica Hamamelis Compuesta; Bioactiv E; Bioactiv R; Grippakit; Ikoplex No 12; *Cz.*: Angin-Heel S; Drosetux; Homeogene 9; Lehnigrip†; Paragrippe; Traumeel; Zeel Compositum; Zeel Salbe†; *Fr.*: Abbe Chaupitre no 10†; Abbe Chaupitre no 13; Abbe Chaupitre no 15†; Abbe Chaupitre no 25†; Abbe Chaupitre no 30†; Acidum Phosphoricum Compose†; Aconitum Compose†; Actheane; Arnica Complexe no 1; Arthro-Drainol; Boripharm No 1†; Calendula Complexe No 89; Crataegus Complexe No 15; Dolisedal†; Drosera Compose; Drosetux; Echinacea Complexe No 40; Gelsemium Complexe No 70; grippe†; Homeofortil†; Homeogene 41†; Homeogene 9; Hypericum Complexe No 26; Kalium Iodatum Complexe No 84†; L

52; Natrum Carbonicum Complexe No 10†; Oenanthe Crocata Complexe No 78; Paragrippe; Poconeol no 61†; Rheumadoron; Rhododendron Complexe No 42†; Sepia Compose; Soludor; Sportenine; Symphytum Complexe No 48†; Tabacum Compose; Veino-Drainol†; Veinosium†; Zincum Cyanidum Complexe No 101†; *Ger.*: Aderplus spezial Dr Hagedorn†; Arnica comp/Apis†; Arnica Comp; Arnica Oligoplex; Arnica/Betula comp; Arnica/Symphytum comp; Arnicarell; Aurum-Gastreu S R2; Capillaron Vertigo; Cardioselect N; Cefadolor Arnica Komplex†; Cefadybasin SE†; Cerebral-Do; Chirofossat; Convallysan M; Corvipas SL; Derivatio H; Derivatio; Goldtropfen S; Inffer N; Infigripp; Infihepan; Jowidarmin; Jsoskleran; K 1000; Kattwicor; Lowe-Komplex Nr 10; Mandragora comp; Myonasan; Odonton-Echtroplex; Ossidal; Pascoe-Agil HOM; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; Plantacard N; Regenaplex Haut G; Regenaplex Haut W; Rheumodoron 102 A; Rheumodoron 1; Roth's RKT Tropfen; Roth's Rotacard; Ruta-Gastreu N R55; Santa Flora S; Secalosan N; Strophanthus comp; Symphytum Rowo†; Trauma SL; Traumakatt; Traumeel S; Uwobletten Arteriosklerose-Complex†; Varicylum N; Venen-Komplex Ho-Fu-Complex; veno-loges N; Venokatt; Wecesin; Wibotin HM; Zeel comp; *Hung.*: Angin-Heel; Aurumheel; Drosetux; Homeogene 9; Traumeel; Zeel; *Neth.*: Achillite; Apo-Rheum†; Arniflor; Arnigel†; Arnilite; Artifleur; Auriculite; Cephalite; Combudoron; Ischilite; Gynaelite; Homeocare Vasco; Homeogene 9†; Muscle Care; Myamolite; Omnilite; Paragrippe†; Phonix Hydrargyrum; Phonix Solidago comp; Reudol; Rhumeel; Sportenine†; Traumeel H; Traumeel S; Venafleur; Zeel comp N; *Port.*: Homeogene 9; Paragrippe; *Rus.*: Анабар (Анабар); Aurum Plus (Аурум-Плюс); Memoria (Мемория); Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Pumpan (Пумпан); Repisan (Реписан); Traumeel S (Траумель С); Zeel T (Цель Т); *S.Afr.*: Rheumadoron†; Traumeel S; *Switz.*: Arnigel; Contusin; Drosetux; Exsepta; Homeogene 9; Nelsons Traumatica†; Regenaplex Nr 41a; Regenaplex Nr 86a; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25b; Regenaplex Nr. 31c; Regenaplex Nr. 3; Regenaplex Nr. 49a; Regenaplex Nr. 50b; Regenaplex Nr. 51c; Regenaplex Nr. 88b; Rheuma-Heel; Rheumadoron; Traumeel; *UK*: Combudoron; Frost Cream; Pyrethrum Spray; Rheumadoron; Rheumadoron; WCS Dusting Powder; *Ukr.*: Aurocard (Аурокард); Memoria (Мемория); Pumpan (Пумпан); Traumeel S (Траумель С); *USA*: Preferred Remedies Aches & Pains; Traumeel; *Venez.*: Traumeel.

Pharmacopoeial Preparations
Ph. Eur.: Arnica Tincture.

Arsenic Triiodide

Arsen. Triiod.; Arsenicum Triioduratum; Arsenii Iodetum; Arsenious Iodide; Arsenium Iodatum; Arsenous Iodide.
AsI_3=455.6
CAS — 7784-45-4.
UNII — 3029988O2T.

Profile

Arsenic triiodide is a trivalent arsenic salt and shares the toxicity of these compounds (see Arsenic Trioxide, below). It was formerly used in the management of some skin conditions.

Homoeopathy
Arsenic triiodide has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Hay Fever; *Austria*: Luffa compositum-Heel; Tartephedreel; *Canad.*: Detox L37; Eczema L87; *Chile*: Plucoccinum; Influk; *Cz.*: Husteel; Luffeel; *Fr.*: Aurum Complexe No 38†; Euphorbium Complexe No 88; Hypericum Complexe No 26; Hypophysis Complexe No 31†; Myosotis Complexe No 63†; Scabiosa Complexe No 87; Sclero-Drainol†; Staphysagria Complexe No 92†; Thuya Complexe No 37; Vespa Complexe No 46†; *Ger.*: Luffeel Comp; Lymphaden Lymphdrusentabletten; Otofren; Rufebran lympho†; Sinasal; Sinusitis Hevert†; Sinusyx; Uwobletten Arteriosklerose-Complex†; *Hung.*: Husteel; Luffeel; *Neth.*: Homeocare Allerlo; Husteel; Luffeel H; Sinufleur; *Switz.*: Regenaplex Nr. 24c.

Arsenic Trioxide *(USAN)*

Acidum Arsenicosum Anhydricum; Anhídrido arsenioso; Arsenii Trioxydum; Arsenic; Arsenic Oxide; Arsénico, trióxido de; Arsenicum Album; Arsénieux, anhydride; Arsenii trioxidum; Arsenious Acid; Arsenous Oxide; White Arsenic. Diarsenic trioxide.
As_2O_3=197.8
CAS — 1327-53-3.
ATC — L01XX27.
ATC Vet — QL01XX27.
UNII — S7V92P67HO.

Pharmacopoeias. In *Jpn.*

Eur. (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Arsenious Trioxide for Homoeopathic Preparations; Arsenii Trioxidum ad Praeparationes Homoeopathicae). A white or almost white powder. Practically insoluble to sparingly soluble in water; it dissolves in solutions of alkali hydroxides and carbonates.

Uses and Administration

Arsenic trioxide is used for induction of remission and consolidation in acute promyelocytic leukaemia (see below). It is given as an intravenous infusion over 1 to 2 hours to patients who are refractory to, or who have relapsed from, conventional therapy with retinoids and antineoplastics; if acute vasomotor reactions occur, the rate of infusion may be slowed and up to 4 hours may be taken. For induction, a dose of 150 micrograms/kg is given once daily until remission occurs; no more than 50 doses should be given (in the USA, the maximum number of induction doses allowed is 60). Treatment for consolidation must begin 3 to 4 weeks after completion of induction (or 3 to 6 weeks in the USA). The dose for consolidation is 150 micrograms/kg once daily given for 25 doses spread over a period of up to 5 weeks; the regimen suggested in the UK is to give the daily dose for 5 days each week followed by 2 days without dosing.

Arsenic trioxide is used in certain Asian herbal remedies. Arsenic anhydride has also been used.

Arsenic trioxide has been widely used as a constituent of weedkillers and sheepdips and as a rodenticide.

Arsenic trioxide and arsenic triiodide (above) were formerly used internally as solutions or externally as ointments in the treatment of various skin diseases, but such use is generally no longer recommended. Such oral solutions were usually prepared with arsenic trioxide and potassium hydroxide or a potassium salt and were known as Fowler's Solution or Potassium Arsenite Solution. Externally, arsenic trioxide has a caustic action.

Homoeopathy
Arsenic trioxide has been used in homoeopathic medicines under the following names: Arsenious trioxide; Arsenici trioxidum; Arsenicum album; Acidum arsenicosum; Arsenicum alb; Ars. alb.

Acute myeloid leukaemias. The use of arsenic trioxide in the management of patients with acute promyelocytic leukaemia (p. 693.1) has been reviewed.[1-5] Remission was achieved in patients who had relapsed despite conventional therapy with retinoids and antineoplastics.[6,7] Arsenic trioxide is also being investigated for postremission therapy and in conjunction with transplantation.[4] Treatment was also successful in newly-diagnosed patients but severe liver toxicity occurred in some cases.[6]

For references to adverse effects occurring in patients receiving arsenic trioxide for acute promyelocytic leukaemia, see under Adverse Effects, p. 2449.1.

1. Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. *Oncologist* 2001; 6 (suppl 2): 11–6.
2. Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development Studies. *Oncologist* 2001; 6 (suppl 2): 22–8.
3. Slack JL, *et al.* Advances in the management of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide. *Oncologist* 2002; 7 (suppl 1): 1–13.
4. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol* 2005; 23: 2396–2410.
5. Leu L, Mohassel L. Arsenic trioxide as first-line treatment for acute promyelocytic leukemia. *Am J Health-Syst Pharm* 2009; 66: 1913–18.
6. Niu C, *et al.* Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* 1999; 94: 3315–24.
7. Soignet SL, *et al.* United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol* 2001; 19: 3852–60.

Multiple myeloma. Arsenic trioxide is under investigation for the treatment of relapsed or refractory multiple myeloma (p. 699.2).

References.

1. Munshi NC. Arsenic trioxide: an emerging therapy for multiple myeloma. *Oncologist* 2001; 6 (suppl 2): 17–21.
2. Munshi NC, *et al.* Clinical activity of arsenic trioxide for the treatment of multiple myeloma. *Leukemia* 2002; 16: 1835–7.
3. Bahlis NJ, *et al.* Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res* 2002; 8: 3658–68.
4. Berenson JR, Yeh HS. Arsenic compounds in the treatment of multiple myeloma: a new role for a historical remedy. *Clin Lymphoma Myeloma* 2006; 7: 192–8.

Myelodysplastic syndromes. The use of arsenic trioxide for the treatment of myelodysplastic syndromes (p. 694.3) is also under investigation.

References.

1. List A, *et al.* Opportunities for Trisenox (arsenic trioxide) in the treatment of myelodysplastic syndromes. *Leukemia* 2003; 17: 1499–1507.
2. Vey N. Arsenic trioxide for the treatment of myelodysplastic syndromes. *Expert Opin Pharmacother* 2004; 5: 613–21.
3. Schiller GJ, *et al.* Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. *J Clin Oncol* 2006; 24: 2456–64.
4. Vey N, *et al.* Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. *J Clin Oncol* 2006; 24: 2465–71.
5. Sekeres MA. New data with arsenic trioxide in leukemias and myelodysplastic syndromes. *Clin Lymphoma Myeloma* 2007; 8 (suppl 1): S7–S12.

Adverse Effects

The toxicity of arsenic compounds varies according to chemical composition, solubility, and valency. Inorganic arsenic compounds are much more toxic than organic compounds and elemental arsenic is the least toxic. Toxicity increases with increasing solubility, and trivalent (arsenite) compounds are more toxic than pentavalent (arsenate) compounds. Arsenic exerts its effects through a variety of pathophysiological mechanisms such as induction of oxidative stress and binding to sulfydryl groups in enzymes, and it has the potential to affect most of the major organ systems in the body; it also induces alteration in gene expression.

Acute poisoning. Estimates of lethal and toxic oral doses vary: the lethal dose of arsenic trioxide has been reported to be around 1 to 3 mg/kg; a dose of 1 mg/kg of arsenic may be lethal in children; acute toxic doses of arsenic compounds have been reported to range from 1 mg to 10 g. Symptoms of acute poisoning occur within 30 minutes to several hours after ingestion and food delays the onset.

Early features of acute arsenic poisoning after ingestion involve the gastrointestinal tract with common symptoms of a metallic or garlic taste, a burning sensation in the mouth, dysphagia, abdominal pain, severe nausea, projectile vomiting, haemorrhagic gastritis, and profuse 'rice-water' diarrhoea leading to hypovolaemic shock; the breath may have an odour of garlic. In the absence of adequate treatment, death can occur within 24 hours of a severely toxic dose. Absorption of arsenic may produce multisystem toxicity days or weeks later, which could include cardiomyopathy, anaemia, leucopenia, skin disorders, acute respiratory distress syndrome, hepatitis, renal failure, encephalopathy, and peripheral polyneuropathy.

Arsenic compounds are irritant and corrosive when inhaled or in contact with the skin or eyes; acute systemic effects may occur after inhalation or skin contact.

Chronic poisoning. Arsenic is widely distributed in the environment: the smelting industry (non-ferrous metals) is a major industrial source of arsenic contamination in the soil, water, and air; mining residues and arsenical pesticides and wood preservatives also contribute to soil and water contamination. Seafood is a source of organic arsenic. Occupational exposure is a potential cause of chronic arsenic toxicity but in the general population, food and drinking water is usually the source of arsenic.

Chronic arsenic poisoning or occupational exposure typically produces varied skin disorders appearing over 10 years, particularly hyperkeratosis, especially affecting the palms and soles, and changes in skin pigmentation. Transverse white lines (Mee's lines) may appear in the nails several weeks after absorption. Gastrointestinal disturbances may occur, although are less likely with chronic exposure. Hypertension, cardiovascular disorders, and diabetes mellitus have been associated with chronic arsenic poisoning. Jaundice may occur as a result of hepatomegaly and portal hypertension may eventually develop. Encephalopathy and peripheral neuropathies may also occur. Arsenic is toxic to the bone marrow and produces blood disorders including leucopenia and aplastic anaemia. Chronic exposure to arsenic has been associated with neoplasms of the skin, lungs, bladder, liver, and kidney. Chronic inhalation of arsenic salts may result in perforation of the nasal septum.

Adverse effects of therapeutic use. Reported adverse effects of arsenic trioxide therapy in patients with acute promyelocytic leukaemia (APL) include leucocytosis, neutropenia, raised liver enzyme values, gastrointestinal disturbances, fatigue, oedema, hyperglycaemia, hypokalaemia, dyspnoea, cough, rashes, pruritus, pyrexia, headaches, paraesthesia, and dizziness. Prolongation of the QT interval and other cardiac arrhythmias have occurred. The so-called 'leucocyte activation syndrome' ('APL differentiation syndrome') similar to one that develops with tretinoin therapy (see Retinoic Acid Syndrome, p. 1726.2) has occurred in some patients. Sudden death has been reported in a few patients.

References,[1-9] including discussion of epidemic toxicity due to arsenic-contaminated drinking water.[4,6-8]

1. Health and Safety Executive. Inorganic arsenic compounds. *Toxic Review 16*. London: HMSO, 1986.
2. Shannon RL, Strayer DS. Arsenic-induced skin toxicity. *Hum Toxicol* 1989; 8: 99–104.
3. Gebel T. Confounding variables in the environmental toxicology of arsenic. *Toxicology* 2000; 144: 155–62.

4. WHO. Arsenic and arsenic compounds. *Environmental Health Criteria 224*. Geneva: WHO, 2001. Also available at: http://www.inchem.org/documents/ehc/ehc/ehc224.htm (accessed 11/04/08)
5. Borak J, Hosgood HD. Seafood arsenic: implications for human risk assessment. *Regul Toxicol Pharmacol* 2007; 47: 204–12.
6. Flora SJ, *et al.* Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review. *J Environ Biol* 2007; 28 (2 suppl): 333–47.
7. Islam LN, *et al.* Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; 42: 1807–14.
8. Guha Mazumder DN. Arsenic and non-malignant lung disease. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; 42: 1859–67.
9. Navas-Acien A, *et al.* Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA* 2008; 300: 814–22.

Adulteration. Arsenical compounds have reportedly been used to "cut" cocaine and symptoms of arsenic poisoning may occur in cocaine abusers.[1] Toxicity due to the presence of arsenic in various ethnic remedies has also been reported.[2-4]

1. Lombard J, *et al.* Arsenic intoxication in a cocaine abuser. *N Engl J Med* 1989; 320: 869.
2. Kew J, *et al.* Arsenic and mercury intoxication due to Indian ethnic remedies. *BMJ* 1993; 306: 506–7.
3. Ernst E, Thompson Coon J. Heavy metals in traditional Chinese medicines: a systematic review. *Clin Pharmacol Ther* 2001; 70: 497–504.
4. Ernst E. Heavy metals in traditional Indian remedies. *Eur J Clin Pharmacol* 2002; 57: 891–6.

Treatment of leukaemia. References[1-4] to and a review[7] of adverse effects in patients receiving arsenic trioxide for the treatment of acute promyelocytic leukaemia, including a report of sudden death occurring in 3 patients in a dose-finding study.[5]

1. Huang SY, *et al.* Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. *Br J Haematol* 1998; 103: 1092–5.
2. Huang CH, *et al.* Complete atrioventricular block after arsenic trioxide treatment in an acute promyelocytic leukemic patient. *Pacing Clin Electrophysiol* 1999; 22: 965–7.
3. Camacho LH, *et al.* Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. *J Clin Oncol* 2000; 18: 2620–5.
4. Ohnishi K, *et al.* Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med* 2000; 133: 881–5.
5. Westervelt P, *et al.* Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood* 2001; 98: 266–71.
6. Cashin R, *et al.* Acute renal failure, gastrointestinal bleeding, and cardiac arrhythmia after administration of arsenic trioxide for acute promyelocytic leukemia. *Am J Health-Syst Pharm* 2008; 65: 941–6.
7. Rust DM, Soignet SL. Risk/benefit profile of arsenic trioxide. *Oncologist* 2001; 6 (suppl 2): 29–32.

Treatment of Adverse Effects

Acute poisoning due to the ingestion of arsenic compounds should be treated by immediate gastric lavage if the patient presents within 1 hour and has not already vomited. Activated charcoal has been used to reduce absorption but is unlikely to be of benefit unless a significant amount of arsenic has been ingested. Intravenous replacement of fluids and electrolytes should be undertaken as necessary to correct dehydration and electrolyte imbalance; pressor agents may be required.

Chelation therapy should be considered in patients with symptoms of arsenic poisoning or with urine-arsenic concentrations above 200 nanograms/mL. In the UK, the therapy of choice for acute arsenic poisoning is unithiol (p. 1579.1) given intravenously initially, especially in cases of gastrointestinal toxicity; stabilised patients can then be changed to the oral route. Oral succimer (p. 1576.3) may be used as an alternative in the absence of gastrointestinal disturbances. Dimercaprol (p. 1549.3) is no longer recommended as first choice therapy in the UK because of its adverse effects. In the USA, dimercaprol, succimer, penicillamine (p. 1567.1), or unithiol have been used as chelation therapy for arsenic poisoning. Courses of chelation therapy should be repeated until urine-arsenic concentrations fall below 50 nanograms/mL and/or there is marked symptomatic improvement. Patients with chronic arsenic poisoning should be removed from the source of contamination as soon as possible. Starting oral chelation therapy will depend on the patient's clinical condition and laboratory results of arsenic in urine, hair, and nails. In the UK, intravenous unithiol is recommended, although the oral route has also been used. Succimer is not considered to be beneficial in chronic arsenic poisoning.

If renal failure occurs haemodialysis may be required.

Poisoning. The treatment of 3 patients who had ingested massive doses of arsenic has been described.[1,2] An adult survived after ingesting 54 g of arsenic trioxide:[1] in addition to standard supportive measures, attempts to remove the arsenic from his gastrointestinal tract included lavage, endoscopic removal, manual removal after gastrotomy, and cleansing enemas, plus chelation therapy. Of 2 siblings who ingested solubilised inorganic arsenic in a pesticide solution,[2] one child (aged 4 months) was estimated to have ingested 428 mg/kg arsenic and died despite aggressive attempts at removal of the arsenic, including chelation therapy, extracorporeal membrane oxygenation, exchange transfusion, and haemodialysis. The other child, aged 2 years, was estimated to have ingested 14.6 mg/kg arsenic, received standard chelation therapy and survived.

1. Duefias-Lasta A, *et al.* Acute arsenic poisoning. *Lancet* 2005; 365: 1982.
2. Lai MW, *et al.* Acute arsenic poisoning in two siblings. *Pediatrics* 2005; 116: 249–57.

Precautions

Patients receiving arsenic trioxide for acute promyelocytic leukaemia should have their ECG, blood sugar, electrolytes, blood count, and coagulation monitored at least twice weekly during induction and at least weekly during consolidation. More frequent monitoring may be needed in clinically unstable patients. Arsenic trioxide should be used with caution in renal impairment since renal excretion is the main route of elimination.

Pharmacokinetics

Water-soluble arsenic acids and their salts are more rapidly absorbed from the gastrointestinal tract than poorly soluble arsenicals such as arsenic trioxide. The absorption of arsenic trioxide is dependent upon the physical form of the compound and coarsely powdered material may be eliminated in the faeces before significant dissolution and absorption can occur. Soluble arsenic salts may also be absorbed after inhalation and through skin.

Once absorbed, arsenic is stored mainly in the liver, kidneys, heart, and lungs, with smaller amounts in the muscles and nervous tissue. About 2 weeks after ingestion, arsenic is deposited in the hair and nails and remains fixed to the keratin for years. It is also deposited in the bones and skin.

Although pentavalent arsenic is reduced to some degree *in vivo* to the more toxic trivalent form, trivalent arsenic is slowly and extensively oxidised to pentavalent arsenic. Both forms are methylated and excreted in the urine, mainly as dimethylarsinic acid, with smaller amounts appearing as monomethylarsonic acid and inorganic arsenic compounds. Although about 60% of a dose may be eliminated in the urine within 8 days, small amounts may continue to be excreted for several weeks after a single dose. Less significant amounts of arsenic are excreted in the faeces and sweat and via the lungs and skin. It is also distributed into breast milk and readily crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Phenasen; *Austria*: Trisenox; *Belg.*: Trisenox; *Braz.*: Trisenox; *China*: Yi Tai Da (伊泰达); *Cz.*: Trisenox; *Fr.*: Trisenox; *Ger.*: Trisenox; *Gr.*: Trisenox; *India*: Arsenox; Arsikem; *Irl.*: Trisenox; *Israel*: Trisenox; *Ital.*: Trisenox; *Jpn*: Trisenox; *Neth.*: Trisenox; *Pol.*: Trisenox; *Port.*: Trisenox; *Spain*: Trisenox; *Thai.*: Asadin†; *UK*: Trisenox; *USA*: Trisenox.

Multi-ingredient Preparations. *Fr.*: Caustinerf Arsenical; Devitasol Arsenical†; Yranicid Arsenical; *Ital.*: Pasta Arsenicale; *Neth.*: Diarrheel S.

Homoeopathic Preparations. *Austral.*: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Hangover Relief; Hay Fever; Homoderma; IBS Eze; Respatona Head Cold; Respatona Sore Throat; Vitatona Energy†; *Austria*: Apozema-Allium Cepa compositum; Daram; Echinacea-Cosmoplex; Erbiode Allergie; Erbiode Haarvital; Famulan; Gastricumeel; Lymphdiaral; Pulsatilla Med Complex; *Canad.*: Allergies; Cat Complex†; Diarrex; Hives; Kids Allergies; Kids' Barache; *Chile*: Bioactiv H; Formula II Especial; Ikoplex No 24; *Fr.*: Abbe Chaupitre no 19†; Abbe Chaupitre no 20†; Abbe Chaupitre no 30†; Abbe Chaupitre no 43†; Abbe Chaupitre no 59†; Abbe Chaupitre no 64†; Abbe Chaupitre no 67†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Abbe Chaupitre no 90†; Agnus Castus Complexe No 2†; Aloe Compose; Boripharm No 12†; Cistus Canadensis Complexe No 86†; Conium Complexe No 36†; Crataegus Complexe No 15; Dermo-Drainol†; Diabene; Diarralia; Euphrasia Complexe No 115; Ferrum Complexe No 29; Gastro-Drainol†; Gelsemium Complexe No 70; Geranium Complexe No 108†; Grindelia Complexe No 58; Kalmia Complexe No 18; L 107; Natrum Carbonicum Complexe No 10†; Nervopax; Nux Vomica Complexe No 49; Oenanthe Crocata Complexe No 78; Pareira Brava Compose; Silicea Complexe No 11; Sulfur Complexe No 12; Tonique Vegetal; Urtica Complexe No 82†; Voxpax; *Ger.*: Allergie-Injektopas; Araniforce arthro; BM Gelo†; Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Curare comp; Entzundungstropfen; Fienin; Gripps; Herniel Injekt; Hewesoor N†; Intercostal-Gastreu; Jowidarmin; Kinolymphat†; Lymphaden Complex; Lymphaden; Lymphdiaral; Neuri-cyl N Ho-Len-Complex; Phonix Silybum spag; Phonix Urtica-Arsenicum spag; Presselin All; Rufebran gastro†; *Neth.*: Allgeno spag; Emvita 21; Emvita 26; Emvita 6; Enulite; Gastricumeel; Kind 0-6 Kindigest; Lymphdiaral; Okugest; *Rus.*: Atma (Атма); Famulan (Фамулан); *Switz.*: Diarrheel S; Gastricumeel; Regenaplex Nr 28a; Regenaplex Nr 28b; Regenaplex Nr 41a; Regenaplex Nr 86a; Regenaplex Nr. 12; Regenaplex Nr. 24b; Regenaplex Nr. 35b; *Ukr.*: Arsenic Comp Iov-Diabet (Арсеник Комп Йов-Диабет); Atma (Атма); Gastrokind (Гастрокинд).

Arsine

Arsenic Trihydride; Arsina; Hydrogen Arsenide; Trihidruro de arsénico.

AsH_3 = 77.95.

CAS — 7784-42-1.

Profile

Arsine is a heavy colourless gas with a garlic-like odour, which has no clinical uses but is an environmental or occupational hazard. It is highly toxic and causes severe haemolysis which may result in acute renal failure. It is potentially toxic below the odour threshold of 0.5 ppm and dangerously toxic after exposure to as little as 3 ppm; there may be a latent period of up to 24 hours after exposure before symptoms develop. Symptoms of arsine gas poisoning include generalised weakness, muscle cramps, thirst, headache, abdominal pain, nausea, vomiting, anorexia, jaundice, bronze skin coloration, haemolytic anaemia, haematuria, oliguria, and anuria. Pulmonary oedema, ECG abnormalities, and peripheral neuropathy have also been reported. Treatment involves exchange transfusions and haemodialysis; dimercaprol and other chelating agents have been used but are of no value in the acute stage and do not prevent haemolysis.

References.

1. Fowler BA, Weissberg JB. Arsine poisoning. *N Engl J Med* 1974; 291: 1171–4.
2. Hesdorffer CS, *et al.* Arsine gas poisoning: the importance of exchange transfusions in severe cases. *Br J Ind Med* 1986; 43: 353–5.
3. Pakulska D, Czerczak S. Hazardous effects of arsine: a short review. *Int J Occup Med Environ Health* 2006; 19: 36–44.

Asafetida

Asafétida; Asafoetida; Asant; Devil's Dung; Gum Asafetida; Асафетида.

ATC Herb — HA03AW5026 (Ferula gummosa: resin); HA03AW5025 (Ferula assafoetida: gum); HR05WA5011 (Ferula assafoetida: resin); HR05WA5012 (Ferula gummosa: resin).

UNII — W9FZA51A5I.

Pharmacopoeias. In *Chin.*

Profile

Asafetida is an oleo-gum resin obtained from various species of *Ferula* (Umbelliferae). It has been used as a carminative and antispasmodic. It was also formerly used as an expectorant. It is used in cooking and is an ingredient of certain foods.

References.

1. Kelly KJ, *et al.* Methemoglobinemia in an infant treated with the folk remedy glycerited asafoetida. *Pediatrics* 1984; 73: 717–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Duiwelsdrekdruppels.

Multi-ingredient Preparations. *India*: Colliwell; Garlill; Lunarex; Tummy Base†; *S.Afr.*: Entressdruppels HM; Stuidruppels; *Thai.*: Corisul; Plataco; Flatulence†; Patarsul; *UK*: Daily Tension & Strain Relief.

Homoeopathic Preparations. *Canad.*: Homeo-Form ST†; Hylands Gas; Kids Calm; Osteel†; Stress L72†; Stress; *Cz.*: Ypsiloheel; *Fr.*: Abbe Chaupitre no 90†; Basilicum Complexe No 96; Cina Complexe No 55†; Homeodose 8†; L 72; Poconeol no 82†; Symphytum Complexe No 48†; *Ger.*: Gnaphalium Injektopas SL; Metaharonga; Nervoregin comp; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rytesthin; Schwoneural N; Sedaphin†; Ypsiloheel N; *Hung.*: Osteoheel; *Neth.*: Discus comp H; Nervival; *Switz.*: Osteoheel.

Asarabacca

Asaro europeo; Bacará; Hazelwort; Rhizoma Asari; Wild Nard; Копытень Европейский.

UNII — H0876AL67A.

NOTE. Asarabacca has also been used as a common name for *Aristolochia clematitis* (see Aristolochia, p. 2447.1).

Profile

Asarabacca is the dried rhizome, roots, and leaves of *Asarum europaeum* (Aristolochiaceae), which is an ingredient of snuffs. It is also an irritant emetic and has been used in rodent poisons. Asarabacca is an ingredient of preparations given for respiratory disorders.

Homoeopathy

Asarabacca has been used in homoeopathic medicines under the following names: Asarum; Asarum europaeum; Asarum eur; Asar. eur.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Asarum Med Complex; Migrenopas†; *Fr.*: Gastro-Drainol†; *Rus.*: Nux Vom-Plus (Нукс Вом-Плюс).

Asbestos

Amianto; Asbesto.

Profile

The name asbestos is applied to several naturally occurring and widely distributed fibrous mineral silicates of the serpentine and amphibole groups. They include amosite (brown asbestos), anthophyllite, chrysotile (white asbestos), and crocidolite (blue asbestos).

Asbestos has properties of heat resistance, insulation, and reinforcement and has been used extensively for heat or electrical insulation, fire protection, in friction materials, and in the construction industry in many materials including cement, pipes, and tiles.

When inhaled, asbestos fibres can cause asbestosis (pulmonary fibrosis), lung cancer, and mesothelioma of the pleura and peritoneum. Mesothelioma has been reported in persons exposed to relatively small amounts of asbestos after an average latent period of 30 to 40 years. An association between occupational exposure and an increased incidence of gastrointestinal, laryngeal, and other cancers has also been reported. Some types of asbestos are more hazardous than others; crocidolite (a member of the amphibole group) is considered to be the most dangerous.

References.

1. Landrigan PJ, *et al.* The hazards of chrysotile asbestos: a critical review. *Ind Health* 1999; 37: 271–80.
2. Browne K, Gee JB. Asbestos exposure and laryngeal cancer. *Ann Occup Hyg* 2000; 44: 239–50.
3. Bourdes V, *et al.* Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000; 16: 411–7.
4. Bolton C, *et al.* Asbestos-related disease. *Hosp Med* 2002; 63: 148–51.
5. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med* 2004; 170: 691–715. Also available at: http://www.thoracic.org/sections/publications/statements/pages/eoh/asbestos.html (accessed 24/07/08)
6. Ulbu T, *et al.* Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet* 2004; 363: 1422–6.
7. Hessel PA, *et al.* Asbestos, asbestosis, and lung cancer: a critical assessment of the epidemiological evidence. *Thorax* 2005; 60: 433–6.
8. O'Reilly KM, *et al.* Asbestos-related lung disease. *Am Fam Physician* 2007; 75: 683–8.
9. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; 62 (suppl 2): ii1–ii19. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Malignant%20Mesothelioma/Guidelines/statement%20on%20malignant%20mesothelioma2007.pdf (accessed 24/07/08)

Ash

Askblad (ash leaf); Chinese Ash (*Fraxinus chinensis*); Common Ash; Esche; European Ash (*Fraxinus excelsior*); Fraxini folium (ash leaf); Frêne; Frêne Élevé (*Fraxinus excelsior*); Frêne, feuille de (ash leaf); Fresno; Jasanový list (ash leaf); Magas kőrisfa levél (ash leaf); Saarenlehti (ash leaf); Uosių lapai (ash leaf); Ясень.

UNII — 9F7B1YGJ59 (Ash); R6KCX5H8I2 (Fraxinus excelsior *bark); RC38362Q7M* (Fraxinus excelsior *leaf); 7G2O12V1NZ* (Fraxinus excelsior *seed).*

Pharmacopoeias. *Chin.* includes Ash Bark (Cortex Fraxini, Qinpi). *Eur.* (see p. vii) includes Ash Leaf.

Ph. Eur. 8: (Ash Leaf; Praxini Folium). The dried leaf of *Fraxinus excelsior* or *Fraxinus angustifolia* (*F. oxyphylla*) or of hybrids of these 2 species or of a mixture. It contains a minimum of 2.5% of total hydroxycinnamic acid derivatives, expressed as chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated with reference to the dried drug.

Profile

The leaf of the European ash (*Fraxinus excelsior*) is included in herbal remedies for the treatment of rheumatic and joint disorders, urinary-tract disorders, and constipation. The leaf of *F. oxyphylla* is also used.

Ash bark has been used to reduce fever and as a tonic.

The bark of the Chinese ash, *F. chinensis* or related species is used in traditional Chinese medicine for disorders including acute dysentery and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Phytodolor; *Austria*: Phytodolor; *Cz.*: Phytodolor†; *Fr.*: Arthritisane†; Arthroflorine†; Azemat†; Boribel Tisane No 17†; Boribel Tisane No 9; Califlorine†; Hydrastart; Mediflor Contre la Constipation Passagere No 7; Mediflor Diuretique No 4†; Mediflor Douleurs Articulaires no 2†; Mediflor no 1; Obeflorine†; Provencale No 2†; Santane O1; Tisane de Sante†; Tisane Provencale no 2†; Tisane Provencale no 6†; Urotisan†; *Ger.*: Phytodolor.

Ashwagandha

Winter Cherry; Витания Снотворная (*Withania somnifera*).

UNII — GD1Z9GY1FW (Withania somnifera); *2HZ95R7082* (Withania somnifera *flower); J337CNM3CW* (Withania somnifera *leaf); V038D626IF* (Withania somnifera *root).*

NOTE. The name Winter Cherry has been applied to several plants including *Physalis alkekengi* (see p. 2590.1) and *Cardiospermum halicacabum*, as well as *Withania somnifera*. Ashwagandha has also been known as Indian ginseng and should not be confused with other ginsengs (see p. 2513.3).

Pharmacopoeias. *US* includes Ashwagandha Root.

Br. includes Withania Somnifera Root.

USP 36: (Ashwagandha Root). Ashwagandha Root is the dried mature roots of *Withania somnifera* (Solanaceae). It contains not less than 0.3% of withanolides calculated on the dried basis, as the sum of withanolide aglycones, calculated as withanolide A, and withanolide glycosides, calculated as withanoside IV. Protect from light and moisture.

BP 2014: (Withania Somnifera Root). The dried mature roots of *Withania somnifera*. It contains not less than 0.01% withaferin A ($C_{28}H_{38}O_6$ = 470.6) and not less than 0.01% withanolide A ($C_{28}H_{42}O_7$ = 502.6). Store in airtight containers.

Profile

The root of ashwagandha, *Withania somnifera* (*Physalis somnifera*) (Solanaceae), has traditionally been used in Ayurvedic medicine and is included in herbal preparations for many conditions. The berries are also used.

References.

1. Kulkarni SK, Dhir A. *Withania somnifera*: an Indian ginseng. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 1093–1105.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Ad Baby; Cebrotone; Eat Ease; Milano; One All Caps; One BE.

Multi-ingredient Preparations. *Austral.*: Fe-Max; Femi-Nan; Ginsynergy plus Rhodiola; Humulus Compound; Lavandula Compound; Memory and Vitality Formula; Mindac; Thyroid Complex; Ultra Calm; Withania Complex; Withania Compound; Women's D-Stress; *Fr.*: Apaisance†; *Hung.*: Herbadict; Munipyrin; *India*: Abana; Addyzoa; Aptizooom; Arthrella; Arthrill; Artrex; Aswal Plus; Attentio; Daash; Femi Forte; Fortege; G-Advit; G-Calvit; Galakol; Geriforte; Geriforte; Glowone; Gynoset; Herr; Imunocin; Lactare; Laforte; Laviril; M2-Tone; Manoll; Memtone; Mentat; Mentofer; Mezica; Mustong; Nevromine; Ojus; *Ital.*: Euroton; *Malaysia*: 30 Plus†; *Rus.*: Fitovit (Фитовит); Tentex (Тентекс); Verona (Верона); *Singapore*: Artrex; *Ukr.*: Bon-Apetit (Бон-Аппетит); Fitovit (Фитовит); Gynopower (Гинопауэр); Trypsidan (Трипсидан)†; Verona (Верона); *USA*: Adrenoid.

Asparagus

Asperge; Garden Asparagus; Sparrow Grass; Sparrowgrass; Аспаргус; Спаржа.

UNII — Z1EJP3037Z.

NOTE. Distinguish from wild asparagus (see under Shatavari, p. 2614.2).

Pharmacopoeias. In *Fr.*

Profile

The roots and aerial parts of asparagus, *Asparagus officinalis* (Asparagaceae), have diuretic and laxative properties and have been included in herbal preparations for urinary tract disorders and constipation. The young shoots are used as a food stuff and their ingestion is followed by excretion of various sulfur compounds that produce a characteristic strong odour in the urine.

Homoeopathy

Asparagus has been used in homoeopathic medicines under the following names: Asparagus officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Neo-Cleanse; Wild Yam Complex; *Fr.*: Biofirm; *Ger.*: Asparagus-P; *Hung.*: Herbadict; Lactonic; *Jpn*: Jiinkokato; Seihaito; *Rus.*: Fitovit (Фитовит); *UK*: AsParAid; *Ukr.*: Andropower (Андропауэр); Gynopower (Гинопауэр).

Homoeopathic Preparations. *Fr.*: Abbe Chaupitre no 20†; Poconeol no 67.

Aspens

NOTE. The term Aspen has been used variously in the literature and reference sources to denote different species of *Populus* or parts thereof. It is therefore often difficult to determine exactly what is intended when this term has been used. Likewise, the term *Populus*, which is used in botanical classifications to denote a genus of plants, and the name Poplar have been applied to similar plants or parts thereof and care should therefore be taken with medicines that use any of the above terms to describe their ingredients.

Populus Alba

Abele; Álamo Blanco; *Populus alba*; Peuplier Blanc; Silber Pappel; White Poplar.

UNII — Y05EGY83Y4 (Populus alba).

Populus Tremula

Asp; Aspen Poplar; Bævre-Asp; Espe; European Aspen; Haapa; *Populus tremula*; Peuplier Tremble; Quaking Aspen; Zitter-Pappel.

ATC Herb — HN02BA5004 (Populus tremula: *leaf); HG04CW5004* (Populus tremula: *leaf); HC01EB5018* (Populus tremula: *bud); HN02BA5003* (Populus tremula: *bud); HR05WA5044* (Populus tremula: *bud); HN02BA5002* (Populus tremula: *bark); HG04CW5003* (Populus tremula: *bark).*

UNII — U755Q6LFAH (Populus tremula); *5Q01F7TPJJ* (Populus tremula *flowering top).*

Populus Tremuloides

Álamo Temblón; American Aspen; American Poplar; Amerikanische Espe; *Populus aurea*; *Populus tremuloides*; Peuplier Faux-tremble; Quaking Aspen; Tremble; Trembling Aspen; White Poplar.

ATC Herb — HN02BA5007 (Populus tremuloides: *leaf); HG04CW5006* (Populus tremuloides: *leaf); HR05WA5045* (Populus tremuloides: *bud); HN02BA5006* (Populus tremuloides: *bud); HC01EB5019* (Populus tremuloides: *bud); HN02BA5005* (Populus tremuloides: *bark); HG04CW5005* (Populus tremuloides: *bark).*

UNII — MUN0TBE4PE (Populus tremuloides); *5543O0CEID* (Populus tremuloides *bark); 7IIH57D9E0* (Populus tremuloides *leaf).*

Profile

Various species of *Populus* (Salicaceae), such as *P. tremula* and *P. tremuloides*, which are sometimes referred to as aspens, are used for their salicin-rich leaves and bark in herbal medicine for prostate disorders and rheumatic conditions. In some sources the species *P. alba* has been grouped with the aspens.

Homoeopathy

Species of aspen have been used in homoeopathic medicines under the following names: Populus tremuloides, Populus trem.

The flowers of *Populus tremula* are also used in homoeopathic medicines under the following names: Populus tremula, flos; Populus trem, flos.

References.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 29/04/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Phytodolor; *Austria*: Phytodolor; Prostagutt; *Canad.*: Cystoforce†; *Cz.*: Phytodolor†; *Ger.*: Eviprostat N; Phytodolor; Prostamed; *Indon.*: Eviprostat; *Jpn*: Eviprostat; *Singapore*: Eviprostat; *UK*: Gerard House Reumalex; Peerless Composition Essence; Tabritis; *Ukr.*: Prostamed (Простамед).

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Canad.*: Homeodel 15†; *Ger.*: Cysto Hevert; Hewecyst Blasen-Nieren†; Homvio-Rin; Homvio-Rin; Inconturina mono; Prostamed Mikto; Prostarell; Prostata-Entoxin N; Prostata-Gastreu N R25; Urokatt; Urotruw N; Ursinol; *Neth.*: Akutur spag; Cystilite; Homeocare Uro; Reneel H; *Ukr.*: Homvio-Prostan (Хомвио-Простан).

Astragalus

Bei Qi; Chinese Astragalus; Huang Qi; Huangqi; Membranous Milk Vetch (*A. Membranaceus*); Meng Gu Huang Qi (*A. mongholicus*); Milk Vetch; Milkvetch.
UNII — QP4TY1M906 (Astragalus mongholicus); 59DKS0719X (Astragalus mongholicus root); UI7YZ55VS (Astragalus propinquus); 922OP8YUPF (Astragalus propinquus root).

NOTE. Distinguish from *Astragalus gummifer*, the source of Tragacanth (p. 2217.1).

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Astragalus Mongholicus Root). The whole dried root of *Astragalus mongholicus* (*A. membranaceus*) freed from rootlets and rootstock, collected from spring to autumn.

Profile

Astragalus is a large genus of about 3 000 species of herbs and small shrubs belonging to the legume family Fabaceae. Many species carry the common name milkvetch.

The root of *A. membranaceus* (*Phaca membranacea*; *A. propinquus*) is used as a tonic in traditional Chinese medicine where it is known by the name huang qi. The closely related species *A. mongholicus* is used similarly. The taxonomy of some species of *Astragalus* is debatable and some authorities regard *A. membranaceus*, *A. mongholicus*, and *A. propinquus* as the same species whereas others consider them to be two or three separate species.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Echinacea Royale; Masculine Herbal Complex; Olf†; Withania Compound; *Canad.*: Defense; *Ital.*: Eutears; *Jpn*: Bologito; Daibofuto; Hangebyakujutsutemmato; Hochuekkito; Juzentaihoto; Kamikihito; Kihito; Ninjin'yoeito; Ogikenchuto; Seishinrenshiin; Seishoekkito; Shichimotsukokato; Tokiinshi; Tokito; *Malaysia*: Elgucare; NeuroAid; Shine Growell; *Philipp.*: Hemofer; *Rus.*: Raylis (Райлис); *Singapore*: NeuroAid.

Avena

Aven; Avione; Cultivated White Oats; Hafer; Oatmeal; Oats; Овёс.
ATC Herb — HN068X5001 (Avena sativa: fresh herb).
UNII — 8PI54V663Y (oatmeal); Z6J799EAJK (Avena sativa grain).

Pharmacopoeias. *US* includes colloidal oatmeal.

USP 36: (Colloidal Oatmeal). The powder resulting from the grinding and further processing of whole oat grain. When dried at 120 degrees for 4 hours it loses not more than 10% of its weight.

Profile

Avena is the grain of *Avena sativa* (Gramineae). It is used in herbal medicine and is reputed to have sedative activity.

A colloidal fraction extracted from avena is used in the preparation of emollient dermatological preparations.

Whether avenin, a protein present in oats, is harmful to patients with coeliac disease is controversial.

Homoeopathy

Avena has been used in homoeopathic medicines under the following names: Avena sativa; Avena e planta tota; Aven. sat.

References.
1. Haboubi NY, *et al.* Coeliac disease and oats: a systematic review. *Postgrad Med J* 2006; 82: 672–8.
2. Kurtz ES, Wallo W. Colloidal oatmeal: history, chemistry and clinical properties. *J Drugs Dermatol* 2007; 6: 167–70.
3. Garsed K, Scott BB. Can oats be taken in a gluten-free diet? A systematic review. *Scand J Gastroenterol* 2007; 42: 171–8.
4. Butt MS, *et al.* Oat: unique among the cereals. *Eur J Nutr* 2008; 47: 68–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dermopan; *Austral.*: Aveeno Preparations; DermaVeen; Nyal Eczema Relief; *Canad.*: Aveeno Preparations; *Chile*: Dermopan; *Fr.*: Aveeno Preparations; Sensifluid; *Hong Kong*: DermaVeen†; *Ital.*: Avalon; Aveeno Preparations; Emulave; *NZ*: DermaVeen; *Port.*: Aveeno Preparations†; Emulave†; *Singapore*: DermaVeen; *UK*: Aveeno Preparations; *USA*: ActiBath; *Venez.*: Dermopan.

Multi-ingredient Preparations. *Arg.*: Aristaloe; Dermalibour; Dermomega; Epitheliale A-Derma; Epitheliale AH; Exomega; Lactoplus; Proavenal Omegatopic; Purasoft; Valeriana Oligoplex; *Austral.*: Avena Complex†; Calmo†; Dong Quai Complex†; Executive B Stress Formula; For Women Active Woman Formula†; GR² Control Appetite Reducer; Masculine Herbal Complex; Olf†; The Blue One†; Tranquil Night; *Canad.*: Cystoforce†; *Chile*: Cytelium; Dermalibour; Epithelial AH; Exomega Barrera; Exomega; Proaven; *Cz.*: Valofyt Neo†; *Fr.*: A-Derma Lait Solaire†; Apaisance†; Biocarde; Cytelium; Derm'Intim; Dermalibour; Dermalibour; Epitheliale; Eryase†; Exomega; Filigel†; Gonaxine; Saugella Girl; Saugella HydraSerum; *Ger.*: Requiesan†; Vollmers praparierter gruner N; *India*: Elovera; *Indon.*: Menolia†; *Irl.*: Avena Sativa Comp; *Ital.*: Acnaveen; *Mex.*: Aveendix; Bonaven; Fruticoline; Suavene; *Neth.*: Plantival; *Philipp.*: Dermablend Colloidal Oatmeal Lotion; *Pol.*: Sedomix; *Port.*: Micaveen†; *Rus.*: Cedoflor (Седофлор); *S.Afr.*: Avena Sativa Comp†; *Singapore*: Dermavive; Sativa; *Switz.*: Mucilar Avena; The d'avoine verte Vollmers†; *UK*: Avena Sativa Comp; Daily Overwork & Mental Fatigue Relief; Daily Tension & Strain Relief; Napiers Herbal Stress & Sleep Aid; Outlook; *Ukr.*: Herbastress (Гербастресс); Pravenor (Правенор); *USA*: Aveeno Cleansing Bar†; *Venez.*: Avensyl; Bonaven; Cytelium; Dagenol; Epitheliale AH; Exomega; Fiberfull.

Homoeopathic Preparations. *Austria*: Acidum phosphoricum Med Complex; Avena Med Complex; Avena Rihom Komplex†; Globuli gegen Schlafstorungen; Notta; Pasconal; Valerianaheel; *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Alfalfa Tonic; Calms Forte; Comp-Drops 1 Stress†; Comp-Drops 7 Sleepless†; Fatigue; Hepar Compositum; Homeo-Form F†; Homeo-Form I†; Homeo-Form ST†; Hylands Formula C; Hylands Formula CF; Insomnia Passiflora†; Insomnia; Kids Calm; Soludor†; Stress L72†; Stress; Ton 2 Complex†; Valerianaheel Comp†; Vegetal Tonic; *Chile*: Melinerv; *Fr.*: Acidum Phosphoricum Compose†; Cereales Germees; Budyne†; L 72; Passiflora GHL; Sativol†; Slipeol†; Soludor; Stressdoron; Tonique Vegetal; Zincum Cyanidum Complexe No 101†; *Ger.*: Alho-Sedosan; Avena sativa comp†; Cefaneuro; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; Dormosyx; Hepar comp; Infinerval; Jsoskleran; Liquidorm N; Lycoaktin; Nervo-Plantin†; Nervoid N; Nervoregin H; Nervoregin; Neurexan; Neuro-Ginsan N; Pasconal Nerventropfen; Passiflora Complex†; Seda-Do; Sedacalman; Sedakatt; Sedaselect; Sedativa-Injektopas; Thyreo-Injektopas; Tondinel H; Tondinel; *Hung.*: PSY-Stabil; *Neth.*: Hyperilite; PSY-stabil; Sativol†; Weleda Avena Valeriana; *Rus.*: Notta (Нотта); *Switz.*: Nelsons Noctura†; *UK*: Noctura; *Ukr.*: Notta (Нотта); *USA*: Preferred Remedies Sleep.

Avocado

Aguacate; Ahuacate; Alligator Pear; Аллигаторова Груша; Авокадо.
UNII — SD587L369F.

Profile

Avocado, *Persea americana* (*P. persea*; *P. gratissima*) (Lauraceae), is included in herbal preparations mainly for respiratory-tract and hepatic disorders. Several parts of the plant, including the fruit and leaves, have been used for a variety of disorders.

The fruit is a dietary source of vitamin E, vitamin B_6, vitamin K, and iron.

Avocado oil is used topically as an emollient and as a neutral carrier for essential oils in aromatherapy. It may also be taken orally.

Osteoarthritis. A mixture comprising one-third avocado oil and two-thirds soya oil (p. 2092.3), and known as avocado-soybean unsaponifiables (ASU) has been given as a dietary supplement to patients with osteoarthritis; an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that it was safe and possibly effective in reducing pain and problems associated with walking and other daily activities.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Piascledine.

Multi-ingredient Preparations. *Arg.*: Derrumal; *Austral.*: Macro Natural Vitamin E Cream; *Braz.*: Piascledine; *Chile*: Codetol PM; Jarabe Palto Compuesto con Miel Adulto; Jarabe Palto Compuesto con Miel Infantil†; Paltomiel Plus; Paltomiel; Paltomiel; Piascledine; Pulmosina; *Cz.*: Piascledine; *Fr.*: Piascledine; *Ital.*: Piascledine; Pluvio; *Mex.*: Piascledine; *NZ*: Mr Nits; *Pol.*: Piascledine; *Port.*: Biureol†; Nutraisdin; *Rus.*: Piascledine (Пиаскледин); *USA*: Sonafine.

Homoeopathic Preparations. *Fr.*: Poconeol no 25; Poconeol no 76; Poconeol no 7.

Azadirachta

Margosa; Neem; Nim; Ним.
UNII — 3TEBA92UPM (neem extract); G580B439YI (Aazadirachta indica bark).

Pharmacopoeias. In *Br.*

BP 2014: (Azadirachta Indica Leaf). The dried leaf of *Azadirachta indica*. It contains not less than 1.0% of tetranortriterpinoids, expressed as salannin, calculated with reference to the dried drug. Protect from moisture.

Uses and Administration

Azadirachta is the dried stem bark, root bark, and leaves of *Azadirachta indica* (*Melia azadirachta*) (Meliaceae), which has been used as a bitter. It is widely used in South Asia and has been reported to have insecticidal, antimalarial, and spermicidal properties. Azadirachta oil (neem oil, margosa oil) expressed from the seeds has also been used.

References.
1. Prakash A, *et al.* A preliminary field study on repellency of neem oil against *Anopheles dirus* (Diptera:Culicidae) in Assam. *J Commun Dis* 2000; 32: 145–7.
2. Boeke SJ, *et al.* Safety evaluation of neem (*Azadirachta indica*) derived pesticides. *J Ethnopharmacol* 2004; 94: 25–41.
3. Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. *Curr Med Chem Anticancer Agents* 2005; 5: 149–56.
4. Maity P, *et al.* The use of neem for controlling gastric hyperacidity and ulcer. *Phytother Res* 2009; 23: 747–55.

Adverse Effects

Effects on the skin. Report of a patient who developed contact dermatitis of the face and ears 1 week after she started using neem oil for the treatment of alopecia areata.[1]

1. Reutemann P, Ehrlich A. Neem oil: an herbal therapy for alopecia causes dermatitis. *Dermatitis* 2008; 19: E12–E15.

Poisoning. Severe poisoning has occurred in Indian children given neem oil as a remedy for minor ailments.[1]

1. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome. *Lancet* 1981; 1: 487–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Malaysia*: Moz-Away; *UK*: Nice 'n Clear.

Multi-ingredient Preparations. *India*: Flexi-muv†; *Indon.*: Bionam; *Ital.*: Keromicil; Keromicil; *NZ*: Mr Nits; *Philipp.*: Cogent db+; *Rus.*: Pilex (Пилекс); *Singapore*: Hemoglo; *UK*: Dr Johnsons Nit & Lice; Hemocyl; MozzyOff Cocktail; Padma Circosan; *Ukr.*: Pilex (Пилекс).

Azapentacene Sulfonate Sodium

Натрия Азапентацена Полисульфонат.
Disodium 5,12-dihydroquinoxalino[2,3-*b*]phenazine disulfonate.
$C_{18}H_{12}N_4O_6S_2Na_2$=490.4
CAS — 1790-56-3 (azapentacene disulfonic acid); 3863-80-7 (azapentacene disulfonate disodium).

Profile

Azapentacene sulfonate sodium has been used topically in the management of cataracts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Luisar; *Hong Kong*: Quinax; *Indon.*: Pentacin†; *Mex.*: Lutrax; *Philipp.*: Quinax; *Pol.*: Quinax; *Rus.*: Quinax (Квинакс); *Singapore*: Quinax; *Thai.*: Quinax; *Ukr.*: Quinax (Квинакс).

Azintamide *(rINN)*

Azintamida; Azintamidum; Azinthiamide; ST-9067; Азинтамид.
2-[(6-Chloro-3-pyridazinyl)thio]-*N,N*-diethylacetamide.
$C_{10}H_{14}ClN_3OS$=259.8
CAS — 1830-32-6.
UNII — ACZ6L64B4I.

Profile

Azintamide has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Biluen Enzimatico; *China*: Mite (迈特); *Port.*: Colerin-F†; *Spain*: Oragalin Espasmolitico.

Azovan Blue *(BAN)*

Azovanum Caeruleum; Azul azován; Azul de Evans; CI Direct Blue 53; Colour Index No. 23860; Evans Blue; T-1824; Эванс Голубой.

Tetrasodium 1,1'-diamino-8,8'-dihydroxy-7,7'-(2,2'-dimethylbiphenyl-4,4'-diylbisdiazo)di-(naphthalene-2,4-disulphonate); Tetrasodium 6,6'-[3,3'-dimethylbiphenyl-4,4'-diylbis(azo)]bis[4-amino-5-hydroxynaphthalene-1,3-disulphonate].
$C_{34}H_{24}N_6Na_4O_{14}S_4$=960.8
CAS — 314-13-6.
UNII — 45PG892GOT.

Profile

Azovan blue is a dye that has been given intravenously for the determination of blood volume; it is firmly bound to plasma proteins and is slow to leave the circulation. Some patients may have staining of the skin.

Azulene

Atsuleeni; Azulen; Azuleno; Azulenum; Cyclopentacycloheptene; Азулен.
$C_{10}H_8$=128.2
CAS — 275-51-4.
UNII — 82R6M9MGLP.

NOTE. The name 'Azulene' has also been used for several derivatives of azulene including azulene sodium sulfonate, chamazulene, guaiazulene, and sodium gualenate.

Profile

Azulene has been used in preparations for anorectal and skin disorders, and for oral hygiene. The sodium sulfonate salt has been used in preparations for mouth and throat disorders and for dyspepsia; sodium gualenate has also been used in gastrointestinal disorders.

Hypersensitivity. Allergic cheilitis occurred in a patient after long-term use of a toothpaste containing azulene.[1]

1. Balato N, *et al.* Allergic cheilitis to azulene. *Contact Dermatitis* 1985; 13: 39–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel:* Kamil Blue.

Multi-ingredient Preparations. *Arg.:* Domuderm; Ninderm; *Braz.:* Eritrex A; Proctosan; *China:* She Lan (舍兰); Zi Mo (兹末); *Hong Kong:* Eye-Ruby Violet†; *India:* Glutazene; *Israel:* Kamil Blue; Kamil Blue; *Ital.:* AZ 15; *Rus.:* Eucasept (Эвкасепт).

Bacopa

Becopa; Brahmi; Herb of Grace; Thyme Leaved Gratiola; Water Hyssop; Бакона.

Pharmacopoeias. In *Br.* *US* includes Bacopa as well as a powdered form and a powdered extract.

BP 2014: (Bacopa Monnieri). The dried aerial parts of *Bacopa monnieri*. It contains not less than 1.0% w/w of bacopa saponins, expressed as bacopaside II ($C_{47}H_{76}O_8$=769.1-), calculated with reference to the dried drug.

USP 36: (Bacopa). The dried stems and leaves of *Bacopa monnieri* (Scrophulariaceae). It contains not less than 2.5% of triterpene glycosides. Protect from light and moisture.

Profile

Bacopa consists of the dried whole plant, preferably the leaves and stem, of *Bacopa monnieri* (*B. monnieria, Gratiola monnieria, Herpestis monniera, Lysimachia monnieri*) Scrophulariaceae (sometimes placed in Plantaginaceae). It is used in Ayurvedic medicine for a variety of indications, and is included in herbal preparations for memory and cognitive disorders.

References.
1. Anonymous. Bacopa monniera. *Altern Med Rev* 2004; 9: 79–85.
2. Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: an overview. *Phytomedicine* 2005; 12: 305–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.:* KeenMind; PM Branin; PM Golbimac; *Philipp.:* Memo Plus Gold; *UK:* Memory Plus.

Multi-ingredient Preparations. *Austral.:* Bacopa & Ginkgo Compound; Bacopa Complex; Brahmi Super Learning Complex; Ginkgo Brahmi; Mens Dual-Action Multi; Mindac; NA Neurocard; PM Kids Intelligent; PM LifeBrain; Thyroid Complex; Ultra Calm; *Indon.:* Bilotec; *Philipp.:* Memory DD†; Premium Memori Plus; *Rus.:* Dipana (Дипана); Fitovit (Фитовит); *Singapore:* Memomet; *Ukr.:* Fitovit (Фитовит); Intellan (Интеллан); Osteoartisi Max (Остеоартизи Макс); Trypsidan (Трипсидан)†.

Bactericidal Permeability Increasing Protein

Proteína bactericida incrementadora de la permeabilidad; Бактерицидный Белок, Увеличивающий Проницаемость Клеточной Мембраны.

Opebacan *(BAN, USAN, rINN)*

Opébacan; Opebacán; Opebacanum; rBPI-21; Опебакан; 132-L-Alanine-1-193-bactericidal/permeability-increasing protein (human).
CAS — 206254-79-7.

Profile

Bactericidal permeability increasing protein is produced by human leucocytes and possesses both Gram-negative bactericidal and endotoxin-neutralising properties. It also inhibits angiogenesis. Several derivatives have been developed and are under investigation. Opebacan is a modified recombinant fragment of bactericidal permeability increasing protein that is under investigation for the treatment of Crohn's disease and meningococcal septicaemia. Other derivatives of bactericidal permeability increasing protein are under investigation for retinopathies and acne.

Bactericidal permeability increasing protein also possesses antifungal activity.

References.
1. Giroir BP, *et al.* Preliminary evaluation of recombinant amino-terminal fragment of human bactericidal/permeability-increasing protein in children with severe meningococcal sepsis. *Lancet* 1997; 350: 1439–43.
2. Levin M, *et al.* Recombinant bactericidal/permeability-increasing protein (rBPI$_{21}$) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. *Lancet* 2000; 356: 961–7.
3. Levy O. A neutrophil-derived anti-infective molecule: bactericidal/permeability-increasing protein. *Antimicrob Agents Chemother* 2000; 44: 2925–31.
4. van der Schaft DW, *et al.* The antiangiogenic properties of bactericidal/permeability-increasing protein (BPI). *Ann Med* 2002; 34: 19–27.

Barium

Bario; Baryum; Барий.
Ba=137.327
CAS — 7440-39-3.
UNII — V645272HLN (barium ion); 24GP945V5T (barium).

Description. Barium is a soft, highly reactive, silvery-white metal.

Uses and Administration

The soluble barium salts are not used in therapeutics but are widely used in industry. For the uses of barium chloride and barium hydroxide lime, see below. Barium sulfide has been used as a depilatory and barium carbonate was used as a rodenticide. The insoluble barium sulfate (p. 1583.2) is used as a contrast medium.

Homoeopathy

Barium salts have been used in homoeopathic medicines under the following names:

- Barium acetate: Acétate de baryum; Barium aceticum; Bariumacetat; Baryta acetica
- Barium carbonate: Barii carbonas; Barium carbonicum; Baryta Carbonica; Carbonate de baryum
- Barium citrate: Baryta citrica; Citrate de baryum
- Barium iodide: Barii iodidum; Barium iodatum; Bariumiodid; Baryta iodata; Iodure de baryum; Barium jodatum
- Barium oxalosuccinate: barium oxalsuccinum

Other barium salts used in homoeopathy and described elsewhere include: barium chloride (below).

Adverse Effects and Treatment

All barium salts that are water- or acid-soluble are very toxic. The symptoms of barium poisoning arise from stimulation of all forms of muscle and include vomiting, excess salivation, colic, diarrhoea, slow or irregular pulse, hypertension, dysarthria, confusion, dizziness, paraesthesias, vertigo, muscle tremors, seizures, muscular paralysis, and respiratory or metabolic acidosis. Hypokalaemia is common. Renal impairment has been reported. Death from cardiac or respiratory failure may occur.

In acute poisoning, emptying the stomach by lavage is recommended if possible. Magnesium or sodium sulfate may be given to convert barium to insoluble barium sulfate. Hypokalaemia and metabolic acidosis should be corrected and ventilation assisted if necessary. Excretion may be increased by diuresis. Haemodialysis may be used in severe poisoning.

Reports of barium intoxication.

1. Lewi Z, Bar-Khayim Y. Food poisoning from barium carbonate. *Lancet* 1964; ii: 342–3.
2. Diengott D, *et al.* Hypokalaemia in barium poisoning. *Lancet* 1964; ii: 343–4.
3. Gould DB, *et al.* Barium sulfide poisoning: some factors contributing to survival. *Arch Intern Med* 1973; 132: 891–4.
4. Berning J. Hypokalaemia of barium poisoning. *Lancet* 1975; i: 110.
5. Wetherill SF, *et al.* Acute renal failure associated with barium chloride poisoning. *Ann Intern Med* 1981; 95: 187–8.
6. Phelan DM, *et al.* Is hypokalaemia the cause of paralysis in barium poisoning? *BMJ* 1984; 289: 882.
7. WHO. Barium. *Environmental Health Criteria 107.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc107.htm (accessed 24/07/08)
8. Sigue G, *et al.* From profound hypokalemia to life-threatening hyperkalemia: a case of barium sulfide poisoning. *Arch Intern Med* 2000; 160: 548–51.
9. Wells JA, Wood KE. Acute barium poisoning treated with hemodialysis. *Am J Emerg Med* 2001; 19: 175–7.
10. Jacobs IA, *et al.* Poisoning as a result of barium styphnate explosion. *Am J Ind Med* 2002; 41: 285–8.
11. Bahlmann H, *et al.* Acute barium nitrate intoxication treated by hemodialysis. *Acta Anaesthesiol Scand* 2005; 49: 110–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.:* Barium Jodatum Oligoplex.

Homoeopathic Preparations. *Austria:* Barium Med Complex; *Canad.:* Ateria-Heel†; Barijodeel†; Ginkgo-Comp†; Hylands Sore Throat; Itires; Sore Throat; *Chile:* Bioactiv M; Silik; *Fr.:* Badiaga Complexe No 47; Phytogargarisme†; Sabal Serrulata Compose; *Ger.:* Antihypertonicum N†; Antihypertonicum-Tropfen N†; Cefadybasin SE†; Lowe-Komplex Nr 3; Zitronensaurezyklus-Heel; *Neth.:* Bronchilite; Co-Hypert; Gastrifleur; Homeocare keelspray; Lymfelite; Lymphomyosot; Myamolite; *Rus.:* Anabar (Анабар); Aurum Plus (Аурум-Плюс); Phytolacca-Plus (Фитолакка-Плюс).

Barium Chloride

Barii Chloridum; Bario cloruro; Bariumklorid; Bariumkloridi; Baru chlorek; Baryum, chlorure de; Барий Хлорид.
$BaCl_2$=208.2
CAS — 10361-37-2 (anhydrous barium chloride); 10326-27-9 (barium chloride dihydrate).
UNII — 0VKS1DA1T2 (anhydrous barium chloride); EL5G-J3U77E (barium chloride dihydrate).

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Barium Chloride Dihydrate for Homoeopathic Preparations; Barii Chloridum Dihydricum ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble or practically insoluble in alcohol.

Profile

Barium chloride has several industrial uses including the manufacture of pigments and dyes, leather tanning, boiler detergents, water softeners, and aluminium refining.

Barium chloride is a soluble salt and therefore potentially toxic if ingested. Systemic toxicity arising from burns to skin from molten barium chloride has been reported. For the adverse effects and treatment of barium and barium salts, and reference to barium chloride poisoning, see under Barium, above.

Homoeopathy

Barium chloride has been used in homoeopathic medicines under the following names: Barium chloratum; Baryta muriatica; Baryta mur; Bar. mur.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria:* Arnica Med Complex; Secale Med Complex; *Canad.:* HPB Complex†; *Fr.:* Pulmo-Drainol†; Sclero-Drainol†; *Ger.:* RauwolfiaViscomp; *Neth.:* Rinileen†; *Rus.:* Aurum Plus (Аурум-Плюс).

Barium Hydroxide Lime

Bario, cal con hidróxido de; Барциевая Известь.
CAS — 17194-00-2 (anhydrous barium hydroxide); 12230-71-6 (barium hydroxide octahydrate).

Pharmacopoeias. In *US.*

USP 36: (Barium Hydroxide Lime). A mixture of barium hydroxide octahydrate and calcium hydroxide; it may also contain potassium hydroxide. White or greyish-white granules, or coloured with an indicator to show when absorptive power is exhausted. It absorbs not less than 19% of its weight of carbon dioxide. Store in airtight containers.

Profile

Barium hydroxide lime is used similarly to soda lime to absorb carbon dioxide in closed-circuit anaesthetic apparatus. Barium hydroxide lime contains a soluble form

of barium and is toxic if swallowed. For the adverse effects and treatment of barium poisoning, see p. 2452.2.

Precautions. Excessive drying out of barium hydroxide lime in anaesthetic apparatus, which may occur if oxygen flow through the equipment is left on for prolonged periods, can lead to the production of carbon monoxide and the risk of inducing carboxyhaemoglobinaemia in patients undergoing anaesthesia using the apparatus.[1]

1. CSM/MCA. Safety issues in anaesthesia: volatile anesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; 23: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Basil

Albahaca; Basil Herb; Basilic; Basilici Herba; Basilienkraut; Sweet Basil; Базилик.
ATC Herb — HA01WA5002 (Ocimum basilicum: herb); HA03AW5044 (Ocimum basilicum: leaf); HR05YA5016 (Ocimum basilicum: leaf); HD11AX5003 (Ocimum basilicum: leaf); HA03AW5043 (Ocimum basilicum: herb).
UNII — 2U0KZP0FDW.

Pharmacopoeias. In *Fr.*

Profile

The aerial parts of basil, *Ocimum basilicum* (Lamiaceae), are used in preparations for gastrointestinal disorders and as a diuretic. It is also used as a culinary herb.

Basil oil is an essential oil with antiseptic properties. It is used in perfumery and cosmetics and also in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aromadetox†; Aromadigest†; Aromazen†; ***Ger.***: Weleda-Rheumasalbe M†; ***Ital.***: Citrosystem; ***Rus.***: Bronchitussin (Бронхитуссен); Bronchocin (Бронхоцин); Bronchoton (Бронхотон); Travisil (Трависил).

Homoeopathic Preparations. ***Canad.***: Indigestion†; ***Fr.***: Basilicum Complexe No 96; ***Ger.***: Phyto-C.

Bay Oil

Aceite esencial de malagueta; Laurel dulce, aceite esencial de; Myrcia Oil; Oleum Myrciae; Масло Бея.
UNII — 3T5GC5CQ33.

NOTE. Distinguish from Laurel Leaf Oil (Bay Leaf Oil) which is obtained from the leaves of *Laurus nobilis* (Lauraceae).

Profile

Bay oil is a yellow volatile oil that darkens rapidly on exposure to air and has a pleasant odour and spicy taste. It is obtained by distillation from the leaves of *Pimenta racemosa* (Myrtaceae) and probably other allied species. The principal use of bay oil is in the preparation of bay rum, which is used as a hair lotion and as an astringent application. Bay oils from both *P. racemosa* and *Laurus nobilis* are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Aromadetox†; Aromadigest†; Percutalgin Phyto; ***UK***: Adiantine; Medicated Extract of Rosemary.

Bayberry

Árbol de la cera; Bayberry Bark; Candle Berry Bark; Chak-lol; Guanacalá; Huacanalá; Mirto ceroso; Myrica; Wax Myrtle Bark; Восковница Восконосная (*Myrica cerifera*).
UNII — 29B6F0441G (Myrica cerifera); 2VZ27D14UH (Myrica cerifera fruit); L41B20QT0M (Myrica cerifera fruit wax); 58Z237VK03 (Myrica cerifera leaf); S46HJ3710D (Myrica cerifera root bark).

NOTE. Bayberry has also been used as a synonym for bog myrtle (see p. 2458.3).

Profile

Bayberry, the root bark of *Myrica cerifera* (Myricaceae), is used in upper respiratory-tract disorders and as a gargle for sore throat. It has also been used in gastrointestinal disorders, to treat vaginal discharge, and topically on ulcers and sores.

Homoeopathy

Bayberry has been used in homoeopathic medicines under the following names: Myrica cerifera; Myrica; Myri. cer.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: HRF; ***UK***: EP&C Essence; Peerless Composition Essence.

Bearberry

Aguavilla; Bärentraubenblätter; Bearberry Leaves; Busserole; Busserole, feuille de; Gayuba; Liść mą; Medvědicový list; Medveszőlőlevél; Meškauogių lapai; Mjölonrisblad; Ptarmiganberry Leaves; Sianpuolukanlehti; Uva de oso; Uva-Ursi; Uvaduz; Uvae ursi folium; Медвежье Ушко.
ATC Herb — RJ01WB5003 (Arctostaphylos uva-ursi: leaf).
UNII — 37SXO36KR7 (Arctostaphylos uva-ursi); 3M5V3D1X36 (Arctostaphylos uva-ursi leaf).

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

Ph. Eur. 8: (Bearberry Leaf). The whole or fragmented dried leaves of the bearberry, *Arctostaphylos uva-ursi*. It contains not less than 7.0% of anhydrous arbutin, calculated with reference to the dried drug. Protect from light.

Profile

Bearberry has been reported to be a diuretic, bacteriostatic, and astringent and has been used in the treatment of urinary-tract disorders.

Homoeopathy

Bearberry has been used in homoeopathic medicines under the following names: Uva ursi; Uva ur.

Adverse effects. Bilateral bull's-eye maculopathy that developed in a 56-year-old woman was suspected to be due to regular ingestion of uva ursi as a tea over a 3-year period, since uva ursi can inhibit melanin metabolism.[1]

1. Wang L, Del Priore LV. Bull's-eye maculopathy secondary to herbal toxicity from uva ursi. *Am J Ophthalmol* 2004; 137: 1135–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Urocystil; ***Braz.***: Uromed; ***Ger.***: Cystinol Akut; Uvalysat; ***Ital.***: Ginocap; ***Pol.***: Uversan; ***Rus.***: Uriflorin (Урифлорин); ***Ukr.***: Cystinol Akut (Цистинол Акут).

Multi-ingredient Preparations. ***Arg.***: Ajolip; Cellasene†; Herbaccion Antioxidante; KLB6 Fruit Diet; Prostamen; Ripped Max; Varicura; ***Austral.***: Althaea Complex†; Colon Care; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; De Witts New Pills†; Detox Program; Extralife Fluid-Care†; Extralife PMS-Care†; Extralife Uri-Care†; PMT-Eze†; ***Austria***: Uropurat†; ***Canad.***: Bio Renal†; Cellutex; Cystoforce†; Diurenat†; Diuretic Formula; Diuretic Tablets; Eliminex; Entwasserungstee†; Hepaflor†; Herbal Diuretic†; Herbal Diuretic; Salusan†; ***Cz.***: Species Urologicae Planta; Urcyston Planta; Urologicka Cajova Smes; ***Fr.***: Boribel Tisane No 17†; Mediflor Diuretique No 4†; Uromil; Urophytum†; ***Ger.***: Arctuvan; Cystinol N; ***Hung.***: Urogin; Uroherb; ***Israel***: Jungborn†; ***Ital.***: Bionefrol; Ginecistin; Litostop; ***Mex.***: Noxivid†; ***Pol.***: Nefrosept; Urofort; ***Port.***: Rilastil Dermo Solar; ***Rus.***: Diureticae Species No2 (Мочегонный Сбор 2); Herbion Urological Drops (Гербион Урологические Капли); Phytonefrol (Фитонефрол); Urokam (Урокам); ***Singapore***: Disco; ***Spain***: Genurat; ***Switz.***: Demonatur Dragees pour les reins et la vessie†; Dragees S pour les reins et la vessie; Femicin Tisane pour reins/vessie†; Impuls dragees pour la vessie et les reins; Sabrinin dragees pour les reins et la vessie; Strath Gouttes pour les reins et la vessie; Tisane pour les reins et la vessie; Urinex; ***UK***: Antitis; Aqua Ban Herbal; Backache Relief; Backache; Backache; Boots Water Relief; Cascade; De Witt's K & B Pills; Diuretabs; HealthAid Boldo-Plus; HRI Water Balance; Kas-Bah; Lowater; Modern Herbals Water Retention; Potenzia; Prementaid; Sciargo; Tabritis; Uvacin; Watershed; ***Ukr.***: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Uro-Control (Уро-Контрол); Urocran (Урокран); ***USA***: Cardiopress.

Homoeopathic Preparations. ***Canad.***: Goldenrod Combination†; ***Fr.***: Pareira Brava Compose; Urocalm; Uva Ursi Complexe No 9; ***Ger.***: HanoNephrin; Levisticum S; ***Rus.***: Cistoit-GF (Цистоит-ГФ); ***Switz.***: Regenaplex Nr 86a; Regenaplex Nr. 49a.

Beleric Myrobalan

Belleric Myrobalan.

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica*, Beleric Myrobalan, above; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Belerica Fruit). The pericarp of dried ripe fruits of *Terminalia belerica*. It contains not less than 10% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruit of beleric myrobalan, *Terminalia bellirica* (*T. bellerica*; *T. belerica*) (Combretaceae), is used in Ayurvedic medicine for a range of conditions including cough and other respiratory-tract disorders. The unripe fruit is used for constipation while the ripe fruit is used for diarrhoea.

The traditional Ayurvedic medicine triphala is a combination of beleric myrobalan, chebulic myrobalan (p. 2474.3), and Indian gooseberry (p. 2532.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Triphala; ***Hung.***: Munipyrin; ***India***: Flexi-muv†; FN-T-Tus†; ***Philipp.***: Cogent db+; ***Rus.***: Doktor Mom (Доктор Мом); Pilex (Пайлекс); Travisil (Трависил); ***Singapore***: Hemoglo; Imunomet; ***Ukr.***: Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Doktor Mom (Доктор Мом сироп); Eve Care (Ив Кер)†; Septilin (Септилин); Travisil (Трависил); Trypsidan (Трипсидан)†.

Belladonna

Belladon; Belladona; Belladone; Belladone, feuille de (belladonna leaf); Belladonnablad (belladonna leaf); Belladonnablätter (belladonna leaf); Belladonnae folium (belladonna leaf); Belladonnanlehti (belladonna leaf); Deadly Nightshade; Liść pokrzyku (belladonna leaf); Nadragulyalevél (belladonna leaf); Rulíkový list (belladonna leaf); Šunvyšnių lapai (belladonna leaf); Tollkirschen; Белладонна.
ATC — A03BA04.
ATC Vet — QA03BA04.
ATC Herb — HN05CW5002 (Atropa belladonna: leaf); HA03YA5002 (Atropa belladonna: leaf); HA03YA5001 (Atropa belladonna: herb); HN05CW5001 (Atropa belladonna: herb).
UNII — WQZ3G9PF0H (Atropa belladonna); 6GZW20TIOI (belladonna leaf); 6MW97Q6E8M (belladonna radix).

NOTE. Distinguish from Russian belladonna (see Scopolia, p. 2611.3).

Pharmacopoeias. *Eur.* (see p. vii) and *US* include a monograph for Belladonna Leaf. *Chin.* includes Belladonna Herb.

Eur. also includes Prepared Belladonna Leaf, Standardised Belladonna Leaf Tincture, and Standardised Belladonna Leaf Dry Extract.

Jpn includes only Belladonna Root.

Ph. Eur. 8: (Belladonna Leaf; Belladonnae Folium). It consists of the dried leaf, or dried leaf and flowering, and occasionally fruit-bearing, tops of *Atropa belladonna*. It contains not less than 0.30% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine with smaller amounts of hyoscine. It has a slightly nauseous odour. Protect from light.

The BP 2014 directs that when Belladonna Herb, Belladonna Leaf, or Powdered Belladonna Herb is prescribed, Prepared Belladonna Herb shall be dispensed.

Ph. Eur. 8: (Belladonna, Prepared; Belladonnae Pulvis Normatus; Prepared Belladonna Herb BP 2014). It is belladonna leaf powder adjusted to an alkaloidal content of 0.28 to 0.32% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

USP 36: (Belladonna Leaf). It consists of the dried leaf and flowering or fruiting top of *Atropa belladonna* (Solanaceae). It yields not less than 0.35% of the alkaloids of belladonna leaf. When moistened, its odour is slight, somewhat tobacco-like. Avoid long exposure to direct sunlight. Protect powdered Belladonna Leaf from light.

Stability in mixtures. Atropine in belladonna preparations was unstable at alkaline pH and would quickly be degraded in mixtures with a pH above 7.[1] Such mixtures in the BPC 1973 included Aluminium Hydroxide and Belladonna Mixture, Cascara and Belladonna Mixture, and Magnesium Trisilicate and Belladonna Mixture.

1. *PSGB Lab Report P/71/9* 1971.

Uses and Administration

Belladonna has the actions of antimuscarinics (see under Atropine, p. 1310.3). Belladonna herb and its preparations have been used for their antimuscarinic actions in many conditions, including the relief of gastrointestinal and

urinary-tract disorders associated with smooth muscle spasm, but they are generally regarded as an outmoded form of treatment.

Belladonna liniments and plasters have been used as counter-irritants for the relief of pain but there is little evidence that they have a beneficial effect and adverse effects have occurred.

Homoeopathy

Belladonna has been used in homoeopathic medicines under the following names: Atropa bella-donna; Belladonna, radix; Belladonna, rad; Bell.

References.
1. Ulbricht C, *et al.* An evidence-based systematic review of belladonna by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2004; **4:** 61–90.
2. Lee MR. Solanaceae IV: Atropa belladonna, deadly nightshade. *J R Coll Physicians Edinb* 2007; **37:** 77–84.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

References.
1. Mateo Montoya A, *et al.* Acute anticholinergic syndrome from Atropa belladonna mistaken for blueberries. *Eur J Ophthalmol* 2009; **19:** 170–2.
2. Bogan R, *et al.* Plasma level of atropine after accidental ingestion of Atropa belladonna. *Clin Toxicol* 2009; **47:** 602–4.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p. 1312.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Bellanorm; *Ger.*: Belladonnysat Burger†; *Pol.*: Bellapan; *Rus.*: Bellacehol (Беллацехол); *Venez.*: Atroveran.

Multi-ingredient Preparations. *Arg.*: Antipasmol; Benitol; Cascara Sagrada Bouzen; Cascara Sagrada Oligoplex; Dioxicolagol; Gastranil; Hepacur; Hepatodirectol; Opobyl; Passacanthine; *Austral.*: Joint & Muscle Cream; *Belg.*: Saintbois; *Braz.*: Acridin; Broncol†; Bronquidex; Brontoss; Calminex Atleta; Calminex H; Cystex; Ductoveran; Gastrobene; Gastrobene; Gotas Preciosas; Hemofleb; Pilulas Ross; Solvobil; *Canad.*: Bellergal; Cystoforce†; *Chile*: Broncodeina; Ergobelan; Fenokomp 39; Gruben; Ramistos; *China*: Aoweishu (奥谓舒); *Cz.*: Capsicolle; *Fin.*: Tannopon†; *Hung.*: Kefalgin; *India*: Aldiamycin; Ergophen; Gynedol; Magnine; Migranil; *Indon.*: Bellapheen; Spasmal; Spasminal†; Stomadon†; *Israel*: Laxative Compound; *Ital.*: Antiemorroidali†; Antispasmina Colica; *Jpn*: Colgen Kowa for Rhinitis; *Mex.*: Chofabol; Parche Negro Belladona; Reudol; *Pol.*: Alax; Bellergot; Biospasmil†; Cholitol; Hemorol; Kapsiplast; Spasticol; *Port.*: Antispasmina Colica†; Cephyl†; Doce Alivio; Migretil; *Rus.*: Anusol (Анузол); Becarbon (Бекарбон); Bellasthesin (Белластезин); Bellataminal (Беллатаминал); Besalol (Бесалол); Bethiol (Бетиол); Gastroguttal (Гастрогуттал); Solutan (Солутан)†; Theophedrinum-N (Теофедрин-Н); Valocormid (Валокормид); Zelenin (Зеленин); *S.Afr.*: Bennetts Colic Mixture†; Bolus Eucalypti Comp†; *Spain*: Alofedina; Carminativo Juventus; Crislaxo; Dolokey†; Laxante Bescansa Aloico†; Tanagel; *Switz.*: Bromocod N†; Cafergot-PB†; Demo Elixir pectoral N†; Escotussin; Nican†; Phol-Tux; *Thai.*: Belacid; Benera†; Delta Charcoal; Neuramizone; New Gel; Pro ABS; *Turk.*: Bellergal; *UK*: Opazimes; *Ukr.*: Bellalgin (Беллалгин); Bellasthesin (Белластезин); Distonin (Дистонин)†; Gastropin (Гастропин); *USA*: B & O Supprettes No. 15A; B & O Supprettes No. 16A; Bel-Phen-Ergot S†; Bellamine†; Bellergal-S; Butibel; Cafatine-PB; Folergot-DF; Phenerbel-S; *Venez.*: Atrobel; Ervostal; Traveget.

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Calm; Childrens Cough Relief; Childrens Sleep; Earache Relief†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Pain & Fever Relief; Respatona Dry Cough & Nasal Congestion; Respatona Sinus Relief; Respatona Sore Throat; Sedatif†; Snorestop; Sports Ice Joint & Muscle; Teething Relief; *Austria*: Aconitum Med Complex; Apozema Apis compositum; Bolus Eucalypti Comp; Bronchalis-Heel; Cantharis Med Complex; Echinacea-Cosmoplex; Erbiode Regelbeschwerden; Erysidoron Nr 1; Exangina†; Globuli gegen Fieber und Grippe Nr 2; Globuli gegen Halsweh Nr 2; Gripagil Husten- und Bronchialtropfen; Nux Med Complex; Pertudoron†; Schnarchex; Spigelon; Taraxacum Med Complex; Tartephedreel; Tonsan akut; Traumeel; Vocara; *Canad.*: Aches & Pains; Angeel†; Bed Wetting†; Bioactiv N†; Bioactiv R†; Breathe More; Bronkeel†; Calnor†; Camilia; Carduus Plex†; Comp-Drops 5 Expectorant†; Coryzalia; Cough & Cold; Den 141†; Diarrhea; Drosera Complex; Drosera Plex†; Earache; Endoteel†; EnurAid; Erysidoron 1†; Formula DM 210†; Formula ES 211; Homeo-Form R†; Homeovox; Husteel†; Hyalgesic HP†; Hylands Formula E; Hylands Headache; Hylands Kinder-BW; Hylands Kinder-T†; Hylands Sore Throat; Ikoplex 12†; Indigestion†; Insomnia Passiflora†; Ivemax; Kids Cough & Cold Phytux; Kids' Earache; L52 Cough & Cold; Larydol†; Pertudoron 1†; Phytotux H; Roxalia; Sedatil; Sinus Ease; Sinusalia; Sinuspax†; Snore No More; Sore Throat; Spascupreel; Spigelon†; Tee Complex†; Teething; Traumeel; Viburcol; *Chile*: Allium Compuesto; Bioactiv N; Bioactiv R; Bioactiv Z; Grippakit; Ikoplex No 12; Influk; *Cz.*: Angin-Heel S; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Husteel; Lehnigrip†; Paragrippe; Sedatif PC; Traumeel; Viburcol; *Fr.*: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 13; Abbe Chaupitre no 1†; Abbe Chaupitre no 22†; Abbe Chaupitre no 23†; Abbe Chaupitre no 25†; Abbe Chaupitre no 66†; Abbe Chaupitre no 6; Abbe Chaupitre no 88†; Abbe Chaupitre no 91†; Agnus Castus Complexe No 2†; Allium Cepa Compose; Aloe Compose; Angipax; Arnica Complexe no 1; Basilicum Complexe No 96; Baudry; Boripharm No 10†; Boripharm No 12†; Boripharm No 1†; Boripharm No 22†; Boripharm No 31; Cholesterolum Complexe No 112†; Cocculus Complexe No 73; Coryzalia; Diabene; Drosera Complexe No 64; Drosera Compose; Drosetux; Euphrasia Complexe No 115; Formica Rufa Compose; Gelsemium Complexe No 70; Grindelia Complexe No 58; grippe†; Hedera Complexe No 120; Helonias Compose; Homeogene 9; Homeogrippe†; Homeovox; Hypericum Complexe No 26; Ipeca Complexe No 65; Juniperus Complexe No 6; Kalium Iodatum Complexe No 84†; Kalium Muriaticum Complexe No 41†; L 107; L 52; L 8; Mercurius Cyanatus Complexe No 43†; Millefolium Complexe No 7†; Momordica Complexe No 109†; Paragrippe; Passiflora GHL; Pertudoron; Pulsatilla Complexe No 60†; Pulviplasmine†; Rubia Complexe No 3; Santaherba; Scrofularia Compose; Sedatif PC; Sinuspax; Tabacum Compose; Urtica Complexe No 82†; Uva Ursi Complexe No 9; Vespa Complexe No 46†; *Ger.*: Angina-Gastreu S R1; Arnica Oligoplex; Broncho-Entoxin N; Cocculus Oligoplex; Contramutan; Echinacin akut; Entzundungstropfen; Enuroplant N; Erysidoron 1; Febro-cyl L Ho-Len-Complex; Gastritis Complex; Gastro-Pasc; HanoTussan; Heweurat N; Infekt-Komplex L Ho-Fu-Complex; Infigripp; Infihepan; Jutussin; Lithiascyl L Ho-Len-Complex; Mato; Mucosa compositum; Mullersche Tabletten; Original-Tinktur N Truw; Pascorenal-Injektopas; Pascosabal; Pertudoron 1; Phonix Silybum spag; Pulmo Bronchialcomplex; Pulmosan; Schworotox; Solidago Hevert Complex; Stoma-Gastreu S R5; Traumeel S; Ulco-cyl L Ho-Len-Complex; Ventrigutt M; Viburcol N; Weleda Fieber- und Zahnungszapfchen; Wiedimmun N†; *Hung.*: Angin-Heel; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Husteel; Sedatif; Spigelon; Traumeel; Viburcol; *Neth.*: Apo-STOM; Auriculite; Belachin-Gastreu R1; Bronchalis; Chelidonium-Homaccord N; Coryzalia; Cystilite; Echilite; Febrilite; Head Care; Hemorrolite; Homeocare keelspray; Homeogene 9†; Homeovox; Husteel; Jutussin R9; Kind 0-3 Chamodent; Kind 0-6 Kinditherm; Mercurius-Heel; Myamolite; Paragrippe†; Red Skin; Sedatif PC; Snurdim; Tonsiotreen; Traumeel S; Viburcol H; Vinceel H; *Port.*: Coryzalia; Homeogene 9; Homeovox; Paragrippe; Sedatif PC; *Rus.*: Belladonna-Plus (Белладонна-Плюс); Cistoit-GF (Цистоит-ГФ); Coryzalia (Коризалия); Homeostres (Гомеострес); Homeovox (Гомеовокс); Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Tonsan-Akut (Тонзан-акут); Traumeel S (Траумель С); Vocara (Вокара); *S.Afr.*: Chamomilla/Millefolium Comp†; Erysidoron 1†; Pertudoron Drops†; Traumeel S; Viburcol; *Switz.*: Alceprin-N; Bronchalis-Heel; Coryzalia; Drosetux; Homeogene 9; Homeovox; Regenaplex Nr 38b; Regenaplex Nr. 24b; Regenaplex Nr. 3; Sedatif PC; Spigelon; Traumeel; Viburcol N; *UK*: Bolus Eucalypti Comp; Erysidoron 1; *Ukr.*: Coryzalia (Коризалия); Dentokind (Дентокинд); Homeovox (Гомеовокс); Incena (Инцена); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); Vocara (Вокара); *USA*: Preferred Remedies Cold & Flu; Traumeel; *Venez.*: Traumeel.

Pharmacopoeial Preparations

Ph. Eur.: Belladonna Leaf Dry Extract, Standardised; Belladonna Leaf Tincture, Standardised;
USP 36: Belladonna Extract Tablets; Belladonna Extract; Belladonna Tincture.

Bellis Perennis

Bellis; Bruisewort; Common Daisy; Daisy; English Daisy; European Daisy; Gänseblümchen; Kaunokainen; Lawn Daisy; Lawndaisy; Massliebchen; Pâquerette; Petite Marguerite; Tausendschön; Tausendschönchen; Tusensköna; Vellorita.
UNII — 2HU33I03UY (Bellis perennis extract).

Profile

The flowers, leaves, and roots of *Bellis perennis* (Asteraceae) have been given orally in herbal medicine for a variety of disorders and externally for wounds and skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Joint & Muscle Cream.

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Sports Ice Joint & Muscle; *Austria*: Traumeel; *Canad.*: Arnicaid; Bumps and Bruises; Eczema L87; Jet Lag; Traumeel; *Cz.*: Traumeel; Fr.: Calendula Complexe No 89; Scabiosa Complexe No 87; *Ger.*: Delto-cyl Ho-Len-Complex; Ekzem-Entoxin N; Infihepan; Phytocortal; Regenaplex Haut W; Roth's RKT Tropfen; Symphytum Rowo†; Traumeel S; *Hung.*: Traumeel; *Neth.*: Opsonat; Traumeel H; Traumeel S; *Rus.*: Traumeel S (Траумель С); *S. Afr.*: Traumeel S; *Switz.*: Regenaplex Nr 41a; Traumeel; *Ukr.*: Traumeel S (Траумель С); *USA*: Traumeel; *Venez.*: Traumeel.

Bendazol Hydrochloride *(rINNM)*

Bendazol, Chlorhydrate de; Bendazol, hidrocloruro de; Bendazoli Hydrochloridum; Dibazol; Hidrocloruro de bendazol; Бендазола Гидрохлорид.
2-Benzylbenzimidazole hydrochloride.
$C_{14}H_{12}N_2,HCl$=244.7
CAS — 621-72-7 (bendazol); 1212-48-2 (bendazol hydrochloride).

Profile

Bendazol hydrochloride is used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Andipal (Андипал); Cytovir (Цитовир); Papazol (Папазол).

Bentiromide *(BAN, USAN, rINN)*

Bentiromid; Bentiromida; Bentiromidi; Bentiromidum; BTPABA; BT-PABA; E-2663; PFT; Ro-11-7891; Бентиромид.
4-(*N*-Benzoyl-L-tyrosylamino)benzoic acid.
$C_{23}H_{20}N_2O_5$=404.4
CAS — 37106-97-1.
ATC — V04CK03.
ATC Vet — QV04CK03.
UNII — 239IF5W61J.

Profile

Bentiromide has been given orally as a noninvasive test of exocrine pancreatic function (see under Pancreatitis, p. 2580.2), the amount of *p*-aminobenzoic acid and its metabolites excreted in the urine being taken as a measure of the chymotrypsin-secreting activity of the pancreas. Headache and gastrointestinal disturbances have been reported in patients receiving bentiromide. The bentiromide test has given misleading results in patients with gastrointestinal, liver, or kidney disorders, or in patients receiving certain foods or drugs that are excreted as arylamines. Some of these drugs included benzocaine, chloramphenicol, lidocaine, paracetamol, procaine, procainamide, sulfonamides, and some diuretics.

References.
1. Hock FJ, *et al.* Improved specificity of the PABA test with p-aminosalicylic acid (PAS). *Gut* 1987; **28:** 468–73.
2. Puntis JWL, *et al.* Simplified oral pancreatic function test. *Arch Dis Child* 1988; **63:** 780–4.

Benzyl Cinnamate

Benzylu cynamonian; Cinnamein; Бензилциннамат.
Phenylmethyl 3-phenyl-2-propenoate.
$C_{16}H_{14}O_2$=238.3
CAS — 103-41-3.
UNII — V67O3RO97U.

Profile

Benzyl cinnamate is a constituent of various balsams and resins, including Peru balsam (p. 2587.1), to which it has been used similarly. It is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Pulmex Baby; Pulmex†; *Braz.*: Ozonyl; *Irl.*: Sudocrem; *UK*: Sudocrem; *Ukr.*: Sudocrem (Судокрем).

Benzyl Isothiocyanate

Bencilo, isotiocinato de; Benzyl Mustard Oil; Benzylsenföl; Oleum Tropaeoli; Бензилгорчичное Масло; Бензилизотиоцианат.
C_8H_7NS=149.2
CAS — 622-78-6.
UNII — 87U6YOR8Q.

Pharmacopoeias. *Fr.* includes Capucine (*Tropaeolum majus*).

Profile

Benzyl isothiocyanate is an oil obtained from *Tropaeolum majus* (Capuchin cress; common nasturtium) (Tropaeolaceae) that has been given as an antibacterial.

Tropaeolum majus has been used in herbal medicine.

Homoeopathy

Tropaeolum majus has been used in homoeopathic medicines under the following names: Tropaeolum.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Angocin Anti-Infekt N; Nephroselect M.

Homoeopathic Preparations. *Ger.*: Jsostoma S.

Benzyl Mandelate

Benzyl Phenylglycolate; Benzylin; Benzylis Mandelas; Benzylium Amygdalicum; Benzyl-α-mandelate; Mandelsäurebenzylester; Бензил Манделат.

$C_{15}H_{14}O_3$=242.3

CAS — 890-98-2.

UNII — 2QN49PWH71.

Profile

Benzyl mandelate has been used for its antispasmodic actions. It has also been included in preparations with analgesics in an attempt to increase the analgesic effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Spasmo Claim†; *Turk.*: Spalt.

Berberine

Berberina.

5,6-Dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium.

$C_{20}H_{18}NO_4$=336.4

CAS — 2086-83-1 (berberine); 633-65-8 (berberine chloride); 633-66-9 (berberine sulfate).

UNII — 0I8Y3P32UF.

Pharmacopoeias. *Chin.* includes berberine chloride. *Jpn* includes berberine chloride hydrate and berberine tannate. *Viet.* includes berberine chloride dihydrate.

Profile

Berberine is a quaternary alkaloid present in hydrastis, in various species of *Berberis*, and in many other plants. It has been used as a bitter and as a flavour in food and alcoholic drinks. It possesses antimicrobial activity and has also been tried as various salts in some infections.

References.

1. Khin-Maung-U, *et al.* Clinical trial of berberine in acute watery diarrhoea. *BMJ* 1985; 291: 1601–5.
2. Rabbani GH, *et al.* Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. *J Infect Dis* 1987; 155: 979–84.
3. Vennerstrom JL, *et al.* Berberine derivatives as antileishmanial drugs. *Antimicrob Agents Chemother* 1990; 34: 918–21.
4. Phillipson JD, Wright CW. Medicinal plants in tropical medicine: 1 Medicinal plants against protozoal diseases. *Trans R Soc Trop Med Hyg* 1991; 85: 18–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Murine; *China*: Si Na Ge (斯娜格).

Multi-ingredient Preparations. *Braz.*: Neo Quimica Colirio†; Visazul; Visolon; *Fr.*: Sedacollyre†; *Hong Kong*: Berber CO†; *UK*: Hemocyl.

Bergamot Oil

Bergamot Essence; Bergamota, aceite esencial de; Essencia de bergamota; Oleum Bergamottae; Бергамотное Масло.

UNII — 39W1PKE3JI.

Pharmacopoeias. In *Fr.* and *It.*

Uses and Administration

Bergamot oil is a greenish or brownish-yellow volatile oil with a characteristic fragrant odour and a bitter aromatic taste, obtained by expression from the fresh peel of fruit of *Citrus bergamia* (Rutaceae). Constituents include linalyl acetate and 5-methoxypsoralen (p. 1714.1).

Bergamot oil is used in perfumery and as a flavour in Earl Grey tea. It has been included in some preparations for upper respiratory-tract disorders and hyperhidrosis. It is also used in aromatherapy.

Adverse Effects

Photosensitivity reactions have occurred following the topical use of preparations containing bergamot oil.

Effects on the muscles. Muscle cramps have been reported[1] in a patient who drank up to 4 litres of 'Earl Grey' tea daily.

1. Finsterer J. Earl Grey tea intoxication. *Lancet* 2002; 359: 1484.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Nopucid Bio Citrus; *Ital.*: Bergacid†; *Philipp.*: Kamillosan M; *Switz.*: Perskindol Classic.

Beta-glucans

Beta-glucani; Beta-glucanos; Betaglukaner; β-D-Glucans; β-Glucans; Бета-глюканы.

CAS — 39464-87-4 (betasizofiran); 9013-94-9 (chrysolaminaran); 104074-36-4 (grifolan); 54724-00-4 (curdlan); 9008-22-4 (laminaran); 9037-88-1 (pachyman); 51052-65-4 (paramylon); 159940-37-1 (pleuran); 9010-72-4 (zymosan).

Pharmacopoeias. In *US*.

USP 36: (Beta Glucan). It is obtained by extraction from the cell wall of fermented and thermally processed *Saccharomyces cerevisiae*. It is comprised mainly of β-(1,3)/(1,6) branched glucan polymers. Small amounts of β-(1,6)-glucan and chitin are also expected to be present in the final product. It contains not less than 70% beta glucan, calculated as glucose after enzymatic hydrolysis, on the dried basis. Store in airtight containers. Protect from light.

Profile

Beta-glucans are a heterogeneous group of naturally occurring polysaccharides consisting of a backbone of β-1→3 linked D-glucopyranosyl moieties to which some D-glucopyranosyl moieties are randomly connected by β-1→6, β-1→3, or β-1→4 linkages as side-chains or branches.

There are numerous beta-glucans and their physical characteristics, such as solubility, and their biological activities vary according to the length of the main chain, the type and degree of branching, and the length of the side-chains. Common sources include: yeasts, mushrooms (reishi, shiitake, maitake) and other fungi; seaweeds and other algae; cereals (oats, barley); and bacteria. There can be considerable variation in the structure of beta-glucans not only between those derived from different sources but also within different batches of the same source. Unfortunately the literature is often vague as to the nature of the beta-glucan used or fails to state its source.

Some beta-glucans and typical sources include:

Algae:
- Chrysolaminaran (chrysolaminarin; leucosin) (*Chaetoceros muelleri*)
- Paramylon (*Euglena gracilis*)

Bacteria:
- Curdlan (*Alcaligenes faecalis*)

Fungi:
- Betasizofiran (scleroglucan) (*Athelia rolfsii; Sclerotium glucanicum; Sclerotium rolfsii*)
- Glomerellan (*Glomerella cingulata*)
- Grifolan (*Grifola frondosa*; maitake)
- Lentinan (*Lentinula edodes*; shiitake; see p. 2543.2)
- Pachyman (*Wolfiporia extensa; Poria cocos*)
- Pleuran (*Pleurotus ostreatus*)
- Polysaccharide-K (*Trametes versicolor; Coriolus versicolor*; see p. 2594.1)
- Sizofiran (*Schizophyllum commune*; see p. 857.2)

Seaweeds:
- Laminaran (Laminarin) (*Laminaria digitata; Laminaria hyperborea*; see p. 2540.1)

Yeasts:
- PGG-glucan (*Saccharomyces cerevisiae*)
- Macrogard (*Saccharomyces cerevisiae*)
- Zymosan (*Saccharomyces cerevisiae*)

Many beta-glucans are reported to have immunomodulating activity and some such as lentinan, polysaccharide-K (a beta-glucan protein complex), and sizofiran are used as adjuncts in the treatment of malignant neoplasms. Others are being studied in various diseases where manipulation of the immune system would be of benefit or as adjuncts in the management of diabetes. Some beta-glucans are promoted as dietary supplements.

It has been reported that soluble beta-glucans tend to be stronger immunostimulants than insoluble ones and modification of the glucan side-chain to produce derivatives such as carboxymethylated compounds has been reported to increase activity.

References.

1. Akramienė D, *et al.* Effects of β-glucans on the immune system. *Medicina (Kaunas)* 2007; 43: 597–606.
2. Chen J, Raymond K. Beta-glucans in the treatment of diabetes and associated cardiovascular risks. *Vasc Health Risk Manag* 2008; 4: 1265–72.
3. Soltanian S, *et al.* Beta-glucans as immunostimulant in vertebrates and invertebrates. *Crit Rev Microbiol* 2009; 35: 109–38.
4. Novak M, Vetvicka V. Glucans as biological response modifiers. *Endocr Metab Immune Disord Drug Targets* 2009; 9: 67–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Decon Nasale; Evacream; Glucanet; Immuwash; Viscoblast Mono; *Turk.*: Imuneks.

Multi-ingredient Preparations. *Braz.*: Minesol; *Fr.*: Herpclair; *Ital.*: Biorag; Edodes; Glucanoos; Immun-up Junior; Immun-up; Imoviral Junior; Imoviral; Linfoflu; Proctocella Complex; Rinotrofina C; Ripavir; Viscoblast; *Singapore*: Bios Life; *USA*: Better Cholesterol.

Betahistine *(BAN, rINN)*

Betahistiini; Betahistin; Betahistina; Bétahistine; Betahistinum; Бетагистин.

N-Methyl-2-(2-pyridyl)ethylamine.

$C_8H_{12}N_2$=136.2

CAS — 5638-76-6.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — X32KK4201D.

Betahistine Hydrochloride *(USAN, rINNM)*

Betahistiinidihydrokloridi; Betahistin Dihidroklorür; Betahistina, hidrocloruro de; Betahistin-dihydrochlorid; Betahistindihydrochlorid; Betahistindihydroklorid; Bétahistine, Chlorhydrate de; Bétahistine, dichlorhydrate de; Betahistine Dihydrochloride (BANM); Betahistini dihydrochloridum; Betahistini Hydrochloridum; Betahistino dihidrocloridas; Hidrocloruro de betahistina; PT-9; Бетагистина Гидрохлорид.

N-Methyl-2-(2-pyridyl)ethylamine dihydrochloride.

$C_8H_{12}N_2.2HCl$=209.1

CAS — 5579-84-0.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — 49K58SMZ7U.

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

Ph. Eur. 8: (Betahistine Dihydrochloride). A white to slightly yellow, very hygroscopic, powder. Very soluble in water; soluble in alcohol; practically insoluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

USP 36: (Betahistine Hydrochloride). A white to almost yellow, very hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; practically insoluble in isopropyl alcohol. pH of a 10% solution in water is between 2.0 and 3.0.

Betahistine Mesilate *(BANM, rINNM)*

Betahistiinimesilaatti; Betahistina, mesilato de; Betahistindimesilat; Betahistin-dimesylát; Bétahistine, Mésilate de; Betahistine Mesylate; Betahistini Dimesilas; Betahistini mesilas; Betahistinmesilat; Betahistino mesilatas; Betahisztin-mezilát; Mesilato de betahistina; Бетагистина Мезилат.

N-Methyl-2-(2-pyridyl)ethylamine bismethanesulphonate.

$C_8H_{12}N_2.(CH_4O_3S)_2$=328.4

CAS — 54856-23-4.

ATC — N07CA01.

ATC Vet — QN07CA01.

UNII — X1L0E3R43Y.

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

Ph. Eur. 8: (Betahistine Mesilate). A white or almost white, crystalline, very hygroscopic powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in isopropyl alcohol. A 10% solution in water has a pH of 2.0 to 3.0. Store in airtight containers.

Uses and Administration

Betahistine is an analogue of histamine and is claimed to improve the microcirculation of the labyrinth resulting in reduced endolymphatic pressure. It is used to reduce the symptoms of vertigo (p. 612.3), tinnitus (p. 1990.1), and hearing loss associated with Ménière's disease (p. 611.2).

Betahistine is given orally as the hydrochloride or mesilate. The usual initial dose of the hydrochloride is 16 mg three times daily taken preferably with meals; maintenance doses are generally in the range of 24 to 48 mg daily. Betahistine mesilate is used in similar doses.

References.

1. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. *CNS Drugs* 2001; 15: 853–70.

2. James A, Burton MJ. Betahistine for Ménière's disease or syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 30/05/06).
3. Della Pepa C, *et al.* Betahistine in the treatment of vertiginous syndromes: a meta-analysis. *Acta Otorhinolaryngol Ital* 2006; 26: 208–15.
4. Phillips JS, Prinsley PR. Prescribing practices for betahistine. *Br J Clin Pharmacol* 2008; 65: 470–1.
5. Barak N. Betahistine: what's new on the agenda? *Expert Opin Invest Drugs* 2008; 17: 795–804.

Adverse Effects

Gastrointestinal disturbances, headache, rashes, and pruritus have been reported.

References.

1. De Riu G, *et al.* An elderly female patient with tardive oromandibular dystonia after prolonged use of the histamine analog betahistine. *J Clin Neurosci* 2010;.

Precautions

Betahistine should not be given to patients with phaeochromocytoma. It should be given with care to patients with asthma, peptic ulcer disease, or a history of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Betaserc; Meniex; Microser; Ronistina; Travelmin; *Austral.*: Seniere; Seniere; Serc; *Austria*: Bestin; Betaserc; *Belg.*: Betahistop†; Betaserc; Docbetahi†; *Braz.*: Betaserc; Labirin; *Canad.*: Serc; *Chile*: Microser; Vasomotal; *China*: Merislon (敏使朗); Xi Qi Ting (西其汀); *Cz.*: Avertin; Bestin; Betaserc; Emperin; Marbeta; Microser; Polvertic; Vertibetis; Vertisan; Zenostig; *Denm.*: Betaserc; Serc; *Fin.*: Acuver; Betaserc; *Fr.*: Betaserc; Extovyl; Lectil; Serc; *Ger.*: Aequamen; Betavert; Vasomotal; *Gr.*: Antivom; Betaserc; Betavert; Katabexin; Ribrain; Riva; *Hong Kong*: Alfinor; Beta-Synto; Betaserc; Meniero†; Merislon; *Hung.*: Acuver; Betagen; Betarevin; Betaserc; Elven; Emperin; Microser; Polvertic; Zenostig; *India*: Arotin; Balanse; Betahist; Betavert; Biobet; Carelet; Divert; Hestin-B; Histavert; Histigo; Hybet; Intrabet; Invert; Meni; Nanovert; Neuvert; Oshvert; Vertin; *Indon.*: Betaserc; Darvon; Histigo; Merislon; Mertigo; Noverty; Vastigo; Vercure; Versilon; Vertex; *Irl.*: Betahecon; By-Vertin; Serc; Vertigon; *Israel*: Agiserc; Betistine; *Ital.*: Betaserc; Fortamid; Microser; Sincrover; Vertiserc; *Jpn*: Merislon; *Malaysia*: Alfinor; Betaserc; Merislon; *Mex.*: Serc; *Neth.*: Betabare; Betakele; Betakile; Betakolet†; Betakule; Betalane; Betalase; Betalene; Betalese; Betaline†; Betalose; Betalune; Betaluse; Betaravet†; Betareze; Betarive; Betarove; Betaruvet†; Betaserc; Betazela; Divetrin; Marbeta; Polvertic; Zenostig; *NZ*: Serc; Vergo; *Philipp.*: Exigo; Merislon; Normini; Serc; Verdiz; Verist; Vert; Vertegra; Vertilate; *Pol.*: Betalan; Betanil; Betaserc; Histigen; Histimerck; Lavistina; Microser; Neatin; Polvertic; Verhist; Vertigen; Vertix; Vestibo; Zenostig; *Port.*: Betaserc; Nucleus†; *Rus.*: Asniton (Асниton); Betacentrine (Бетацентрин); Betannorm (Бетаноpм); Betaserc (Бетасерк); Betaver (Бетавер); Microser (Микрозер); Tagista (Тагиста); Vasoserc (Вазосерк); Vestibo (Вестибо); *S.Afr.*: Serc; *Singapore*: Betaserc; Merislon; *Spain*: Fidium; Serc; *Switz.*: Betaserc; *Thai.*: Behistin; Betahis; Betahist-B†; Betris; Merislon; Merlin; Mertigo; Serc; Stei; *Turk.*: Betaris; Betaserc; Betateva; Medisense; Vasoserc; Vertiserc; Vestibo; *UK*: Serc; *Ukr.*: Betagis (Бетагис); Betanorm (Бетаноpм); Betaserc (Бетасерк); Vasoserc (Вазосерк); Vestibo (Вестибо); Vestinorm (Вестинорм); *Venez.*: Microser; Serc.

Pharmacopoeial Preparations

BP 2014: Betahistine Dihydrochloride Tablets.

Betaine

Betaína; Glicina Betaina; Glicolol Betaina; Glycine Betaine; Glycocoll Betaine; Lycine; Trimethylglycine; Бетаин.

(Carboxymethyl)trimethylammonium hydroxide inner salt.

$C_5H_{11}NO_2$=117.1

CAS — 107-43-7.

ATC — A16AA06.

ATC Vet — QA16AA06.

UNII — 3SCV180C9W.

Betaine Hydrochloride

Betainihydrokloridi; Betaína, hidrocloruro de; Betainhydroklorid; Betaini Hydrochloridum; Trimethylglycine Hydrochloride; Бетаина Гидрохлорид.

(Carboxymethyl)trimethylammonium hydroxide inner salt hydrochloride.

$C_5H_{11}NO_2.HCl$=153.6

CAS — 590-46-5.

ATC — A09AB02.

ATC Vet — QA09AB02.

UNII — JK8U8K4D6K.

Pharmacopoeias. In *US*.

USP 36: (Betaine Hydrochloride). A white crystalline powder. Soluble in water and in alcohol; practically insoluble in chloroform and in ether. A 25% solution in water has a pH of 0.8 to 1.2.

Profile

Betaine is used as a methyl donor to remethylate homocysteine to methionine in the treatment of patients with homocystinuria (see Amino Acid Metabolic Disorders, p. 2042.2). It is given orally in a usual dose of 3 g twice daily. Doses are adjusted according to plasma-homocysteine concentrations; up to 20 g daily has been required in some patients. For doses in children, see below.

Severe cerebral oedema and hypermethioninaemia have been reported in a few patients, and it is recommended that plasma-methionine concentrations should be monitored at the start of betaine treatment and periodically thereafter. Patients being treated for cystathionine beta-synthase deficiency may pose particular problems because betaine may further raise their already elevated methionine concentrations increasing the risk of cerebral oedema.

Betaine has also been used as a variety of salts in preparations for liver and gastrointestinal disorders. The hydrochloride has been given as a source of hydrochloric acid in the treatment of hypochlorhydria.

Administration in children. In the UK, betaine is given orally to children under 10 years of age in a usual daily dose of 100 mg/kg in 2 divided doses, adjusted according to response up to a maximum of 150 mg/kg daily. However, in the USA, licensed product information recommends this lower dose only for children under 3 years of age, and recommends the usual adult dose (see above) for children over 3 years.

Adverse effects. References.

1. Devlin AM, *et al.* Cerebral edema associated with betaine treatment in classical homocystinuria. *J Pediatr* 2004; 144: 545–8.

Homocystinuria. References.

1. Smolin LA, *et al.* The use of betaine for the treatment of homocystinuria. *J Pediatr* 1981; 99: 467–72.
2. Wilcken DEL, *et al.* Homocystinuria—the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983; 309: 448–53.
3. Holme E, *et al.* Betaine for treatment of homocystinuria caused by methylenetetrahydrofolate reductase deficiency. *Arch Dis Child* 1989; 64: 1061–4.
4. Anonymous. Betaine for homocystinuria. *Med Lett Drugs Ther* 1997; 39: 12.

Liver disorders. Betaine has also been investigated for the treatment of nonalcoholic steatohepatitis.

References.

1. Miglio F, *et al.* Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis: a double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittelforschung* 2000; 50: 722–7.
2. Abdelmalek MF, *et al.* Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *Am J Gastroenterol* 2001; 96: 2711–7.

Pharmacokinetics. References.

1. Schwahn BC, *et al.* Pharmacokinetics of oral betaine in healthy subjects and patients with homocystinuria. *Br J Clin Pharmacol* 2003; 55: 6–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cystadane; *Austria*: Cystadane; *Belg.*: Cystadane; *Canad.*: Cystadane; *Cz.*: Cystadane; *Denm.*: Cystadane; *Fr.*: Cystadane; *Ger.*: Cystadane; *Irl.*: Cystadane; *Israel*: Cystadane; *Ital.*: Cystadane; *Neth.*: Cystadane; *Norw.*: Cystadane; *Pol.*: Cystadane; *Port.*: Cystadane; *Spain*: Cystadane; *Swed.*: Cystadane; *USA*: Cystadane.

Multi-ingredient Preparations. *Arg.*: Skin Hair & Nails; *Austral.*: Betaine Digestive Aid; Digestaid; Digestive Zyme†; *Austria*: Oroacid†; *Belg.*: Digestomen; *Braz.*: Abcler; Anekron; Biohepax†; Chofrafig; Colachofra; Enterofigon; Epocler; Hepalin; Hepatox; Metiocolin Composto; Necro B6; Xantinon Complex; *Canad.*: Digesdyn; Digest; Formula 17605 Diaplex; Formula 3358†; Mega Zyme†; Multi-Zyme†; *Fr.*: Actigess†; Citrarginine†; Hepagrume; Nivabetol†; *Ger.*: Flacar; *Gr.*: Efkalsol; Kloref; *Hong Kong*: Jetepar†; *Hung.*: Betacid; *India*: Homocyst; *Indon.*: DFM; *Ital.*: Citroepatina†; Ri-Donna; *Malaysia*: Enzyme Digest; Jetepar; *Neth.*: Gastrobul†; *Philipp.*: Jetepar; *S.Afr.*: Kloref†; *Singapore*: Jetepar†; *Switz.*: Halipepsin†; *UK*: Enzyme Digest; Enzyme Plus; Kloref†; Magnesium-B; *Ukr.*: Citrarginine (Цитраргинин); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Clinical Nutrients 50-Plus Men; Mimyx†; Panplex 2-Phase; Sunnie; Tyler Prenatal.

Bethanechol Chloride *(BAN)*

Betanecol, cloruro de; Betanekolikloridi; Betanekolklorid; Bethanecholi Chloridum; Carbamylmethylcholine Chloride; Бетанехола Хлорид.

(2-Carbamoyloxypropyl)trimethylammonium chloride.

$C_7H_{17}ClN_2O_2$=196.7

CAS — 674-38-4 (bethanechol); 590-63-6 (bethanechol chloride).

ATC — N07AB02.

ATC Vet — QN07AB02.

UNII — H4Q8Z2LO84.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Bethanechol Chloride). Colourless or white crystals, or white crystalline powder, usually having a slight, amine-like odour. It is hygroscopic and exhibits polymorphism. Freely soluble in water and in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 5.5 and 6.5. Store in airtight containers.

Stability. References to the stability of oral liquid preparations of bethanechol chloride prepared extemporaneously from tablets.

1. Schlatter JL, Saulnier J-L. Bethanechol chloride oral solutions: stability and use in infants. *Ann Pharmacother* 1997; 31: 294–6.
2. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1998; 55: 1804–9.

Sterilisation. The US manufacturers state that solutions of bethanechol chloride may be autoclaved at 120 degrees for 20 minutes without discoloration or loss of potency.

Uses and Administration

Bethanechol chloride, a choline ester, is a quaternary ammonium parasympathomimetic that mainly exhibits the muscarinic actions of acetylcholine (p. 2003.2). It is not inactivated by cholinesterases so its actions are more prolonged than those of acetylcholine. Bethanechol chloride has little if any nicotinic activity and is used for its actions on the bladder and gastrointestinal tract. It has been used as an alternative to catheterisation in the treatment of urinary retention and has also been used for gastric atony and retention, abdominal distension following surgery, congenital megacolon, and gastro-oesophageal reflux disease.

Bethanechol chloride is given in usual doses of 10 to 50 mg orally up to 4 times daily, but dosage must be adjusted individually. Doses should be taken on an empty stomach. Bethanechol has also been given subcutaneously. For a warning to avoid intravenous or intramuscular use, see under Precautions, below.

Decreased gastrointestinal motility. Parasympathomimetics such as bethanechol enhance gastric contractions and increase intestinal motility and form just one of many treatments that have been used in conditions associated with decreased gastrointestinal motility (p. 1805.2).

Gastro-oesophageal reflux disease. Prokinetic drugs such as bethanechol have been tried in gastro-oesophageal reflux disease (p. 1807.2).

References.

1. Thanick KD, *et al.* Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. *Ann Intern Med* 1980; 93: 805–8.
2. Saco LS, *et al.* Double-blind controlled trial of bethanechol and antacid versus placebo and antacid in the treatment of erosive esophagitis. *Gastroenterology* 1982; 82: 1369–73.
3. Thanick K, *et al.* Bethanechol or cimetidine in the treatment of symptomatic reflux esophagitis: a double-blind control study. *Arch Intern Med* 1982; 142: 1479–81.
4. Strickland AD, Chang JHT. Results of treatment of gastroesophageal reflux with bethanechol. *J Pediatr* 1983; 103: 311–15.

Urinary incontinence and retention. Bethanechol is one of the parasympathomimetics that have been given to increase detrusor activity in patients with overflow incontinence, but there have been doubts about the efficacy of such treatment (see p. 2349.2). Bethanechol was also one of the parasympathomimetics used in the management of postoperative urinary retention but they have generally been superseded by catheterisation.

References.

1. Finkbeiner AE. Is bethanechol chloride clinically effective in promoting bladder emptying: a literature review. *J Urol (Baltimore)* 1985; 134: 443–9.
2. Kemp B, *et al.* Prophylaxis and treatment of bladder dysfunction after Wertheim-Meigs operation: the positive effect of early postoperative detrusor stimulation using the cholinergic drug betanecholchloride. *Int Urogynecol J Pelvic Floor Dysfunct* 1997; 8: 138–41.
3. Riedl CR, *et al.* Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. *J Urol (Baltimore)* 2000; 164: 2108–11.

Adverse Effects and Treatment

As described for choline esters under Acetylcholine Chloride, p. 2003.2.

Precautions

As described for choline esters under Acetylcholine Chloride, p. 2003.3.

Bethanechol should not be given by the intravenous or intramuscular routes as very severe muscarinic adverse

effects are liable to occur, calling for emergency use of atropine.

Autonomic neuropathy. Patients with autonomic neuropathy might be more susceptible to the adverse effects of bethanechol and they should be started on low-dosage regimens and observed closely for signs of toxicity.[1]

1. Caraco Y, *et al.* Bethanechol-induced cholinergic toxicity in diabetic neuropathy. *DICP Ann Pharmacother* 1990; **24**: 327–8.

Interactions

As for Neostigmine, p. 688.3.

Pharmacokinetics

Bethanechol chloride is poorly absorbed from the gastrointestinal tract. It is not hydrolysed by cholinesterases. At standard doses bethanechol does not cross the blood-brain barrier.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Miotonachol; *Austral.*: Urocarb; *Austria*: Myocholine; *Belg.*: Myocholine; *Braz.*: Liberan; *Canad.*: Duvoid; Myotonachol†; *Ger.*: Myocholine; *India*: Bethacol; Urotone; Urotonin; *Philipp.*: Uriflow; *Switz.*: Myocholine; *Thai.*: Ucholine; Urecholine; *UK*: Myotonine; *USA*: Myotonachol; Urecholine.

Pharmacopoeial Preparations
USP 36: Bethanechol Chloride Injection; Bethanechol Chloride Oral Solution; Bethanechol Chloride Oral Suspension; Bethanechol Chloride Tablets.

Bibrocathol *(rINN)*

Bibrocathin; Bibrocatholum; Bibrocatol; Bibrokatol; Bibrokatoli; Bismuth Tetrabrompyrocatechinate; Tetrabromopyrocatechol Bismuth; Биброкатол.
4,5,6,7-Tetrabromo-2-hydroxy-1,3,2-benzodioxabismole.
$C_6HBiBr_4O_3$=649.7
CAS — 6915-57-7.
ATC — S01AX05.
ATC Vet — QS01AX05.
UNII — 0KJ20H1BLJ.

Profile

Bibrocathol is a bismuth-containing compound that has been applied topically in the treatment of eye disorders, wounds, and burns.

References.

1. Behrens-Baumann W, *et al.* Bibrocathol-Augensalbe ist wirksam bei Blepharitis. Ergebnisse einer randomisierten, doppelblinden, kontrollierten klinischen Studie. *Ophthalmologe* 2006; **103**: 960–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bibrocathol 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 31/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Noviform†; Posiformin; *Swed.*: Noviform; *Switz.*: Posiformin.

Bicyclol

Бициклол.
4,4′-Dimethoxy-5,6,5′,6′-bis(methylene-dioxy)-2-hydroxymethyl-2′methoxycarbonyl biphenyl.
$C_{19}H_{18}O_9$=390.3

Profile

Bicyclol has been used as a hepatoprotectant in the management of hepatitis. It has been given orally in a dose of 25 or 50 mg three times daily for at least 6 months.

References.

1. Liu Q, *et al.* A useful agent for chemoprevention of hepatocellular carcinoma? *Cancer Biol Ther* 2006; **5**: 1674–6.
2. Wu T, *et al.* Bicyclol for chronic hepatitis B. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 01/05/08).
3. Yang X, *et al.* Bicyclol for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 01/05/08).
4. Liu GT. Bicyclol: a novel drug for treating chronic viral hepatitis B and C. *Med Chem* 2009; **5**: 29–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bai Sai Nuo (百赛诺).

Bifendate

Dimethyl 7,7′-dimethoxy-(4,4′-bi-1,3-benzodioxole)-5,5′-dicarboxylate.
$C_{20}H_{18}O_{10}$=418.4
CAS — 73536-69-3.

Pharmacopoeias. In *Chin.*

Profile

Bifendate is derived from schisandra (see p. 2611.2). It is used in Chinese medicine for chronic hepatitis.

Bifendate has been reported to reduce blood concentrations of ciclosporin (see p. 1953.2).

Bile Acids and Salts

Biliares, ácidos y sales; Желчные Кислоты и Соли Желчных Кислот.
CAS — 81-25-4 (cholic acid); 11006-55-6 (sodium tauroglycocholate); 361-09-1 (sodium cholate).

Pharmacopoeias. *Jpn* includes bear bile.

Profile

The principal primary bile acids, cholic acid and chenodeoxycholic acid (p. 2475.1), are produced in the liver from cholesterol and are conjugated with glycine or taurine to give glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid, before being secreted into the bile where they are present as the sodium or potassium salts (bile salts). Secondary bile acids are formed in the colon by bacterial deconjugation and 7α-dehydroxylation of cholic acid and chenodeoxycholic acid, producing deoxycholic acid and lithocholic acid, respectively. Ursodeoxycholic acid (p. 2638.1) is a minor bile acid in man although it is the principal bile acid in *bears*. Dehydrocholic acid (p. 2492.1) is a semisynthetic bile acid.

The total body pool of bile salts is about 3 g, and most of the secreted bile salts are reabsorbed in a process of enterohepatic recycling, so that only a small fraction of this amount must be synthesised *de novo* each day.

Bile salts are strongly amphiphilic; with the aid of phospholipids they form micelles and emulsify cholesterol and other lipids in bile. Oral administration of chenodeoxycholic acid also reduces the synthesis of cholesterol in the liver, while ursodeoxycholic acid reduces biliary cholesterol secretion apparently by increasing conversion of cholesterol to other bile acids. The bile acids (but not the bile salts) also have a choleretic action, increasing the secretion of bile, when given orally.

Chenodeoxycholic acid and ursodeoxycholic acid are given orally in the management of cholesterol-rich gallstones (p. 2639.1) in patients unsuited to, or unwilling to undergo, surgery. Ursodeoxycholic acid is also used in some chronic liver diseases (p. 2638.2) including primary biliary cirrhosis (p. 2638.3).

Preparations containing bile salts have been used to assist the emulsification of fats and absorption of fat-soluble vitamins in conditions in which there is a deficiency of bile in the gastrointestinal tract. Ox bile has also been used in the treatment of chronic constipation. Cholic acid is used for the treatment of inborn errors in primary bile synthesis.

Sodium cholate has been used for its spermicidal properties in barrier contraceptives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Desicol†; *Mex.*: Virulizin; *Rus.*: Festal (Фестал); *S.Afr.*: Biron†; *Ukr.*: Allocholum (Аллохол); *Venez.*: Hepa-Desicol.

Multi-ingredient Preparations. *Arg.*: Bibol Leloup; Bil 13; Bilagol Antigas; Bilidren; Carbogasol Digestivo; Cascara Sagrada Bouzen; Digesplen; Hepatalgina; Nilflux; Opobyl; Veracolate†; Zimerol; *Austral.*: Digestaid; Enzyme; *Austria*: Buccalin; Helopanzym; Intestinol†; Silberne†; *Belg.*: Buccaline†; *Braz.*: B-Vesil†; Dasc†; Figatil; *Canad.*: Artechol†; Articho-Nat; Bicholate†; Colibyl†; Digesdyn; Digestolax; Formula B-1†; Heparticaut†; Lipozyme†; Multi-Zyme†; Regubil; *Chile*: Combizym Compositum†; Flapex E; Hepabil; K.C.M.C; Katin; *China*: Fufang Dan An Pian (复方胆氨片); Wei Tai Kang (谓泰康); *Cz.*: Combizym Compositum†; *Fr.*: Rectopanbiline; *Hong Kong*: Enzyplex; Hepatofalk†; Protectaid; *India*: Cyltabs; Digeplex-T; Dispeptal; Enzovit; Festal; Kamozyme-EP; Livotone; Merckenzyme†; Mumzyme; Papytazyme; *Indon.*: Benozym; Berzymplex; Cotazym Forte; Enzymfort; Enzyplex; Eviprostat; Pankreon Comp; *Israel*: Encypalmed; Protectaid; *Ital.*: Solvobil†; *Malaysia*: Enzyplex†; *Mex.*: Dixiflen; Espaven Enzimatico; Ochozim; Zimeton; *NZ*: Buccaline; *Philipp.*: SG-Glutergen; *Port.*: Fermetone Composto; *Rus.*: Biofestal (Биофестал); Cholenzim (Холензим); Ipental (Ипентал)†; Phereslhal (Ферестал); *Singapore*: Enzyplex; *Swed.*: Combizym Compositum†; *Switz.*: Buccaline; Combizym Compositum; *Thai.*: Combizym Compositum†; Enzyplex†; Patarcolate; Veracolate†; *Turk.*: Platon; Intestinol; Multanzim†; Pankreon Comp; Pankrodigest†; *UK*: Protectaid; *Ukr.*: Choliver (Холивер)†; Festal (Фестал); *USA*: Digepepsin; Panplex 2-Phase; *Venez.*: Combizym Forte; Nutrizym Compositum; Pankreon Compositum; Stamyl.

Homoeopathic Preparations. *Canad.*: Carduus Plex†; *Fr.*: Bilinum Complexe No 113; Hepatodrainol.

Birch Leaf

Abedul, hojas de; Beržų lapai; Betulae Folium; Březový list; Birkenblätter; Björkblad; Bouleau; Bouleau, feuille de; Koivunlehti; Liść brzozy; Nyírfalevél; Silver Birch Leaf; Берёзовый Лист.
ATC Herb — HG04BW5005 (Betula pendula: leaf).
UNII — 5HW39H9KDH.

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

Ph. Eur. 8: (Birch Leaf). The whole or fragmented dried leaves of *Betula pendula* and/or *B. pubescens* as well as hybrids of both species. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), with reference to the dried drug. Protect from light.

Profile

Birch leaf is used in herbal medicine, particularly for urinary-tract disorders. Birch leaf oil has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Betulacur†; Urorenal†; *Hung.*: Salus Diuretic.

Multi-ingredient Preparations. *Arg.*: Sequals G; *Austria*: Blasentee St Severin; Heumann's Blasen- und Nierentee; Rheuma; Solubitrat†; *Canad.*: Bio Renal†; Entschlackungstee N†; Entwasserungstee†; Rheuma Heilkrauter Tee†; *Chile*: Cellenergy; *Cz.*: Fytokliman Planta; Reduktan; Species Urologicae Planta; Urologicka Cajova Smes; *Fr.*: B.O.P.; Depuratum; Detoxifiance; Drainactil†; Mediflor Douleurs Articulaires no 2†; Silibiol; Urotisan†; *Ger.*: Antihypertonicum S; BioCyst†; Biofax†; Dr Wiemanns Rheumatonikum†; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Heumann Blasen- und Nierentee Solubitrat uro; Hevert-Blasen-Nieren-Tee N†; Nephroselect M; Renob Blasen- und Nierentee†; *Hung.*: Kilo-Nit; Mensesyl; Urogin; Uroherb; *Ital.*: Flebonorm; Gemiol Plus; Ginoday; Linfonorm; Lipaven; Listerine Fresh Citrus; Slimmer Plus; *Pol.*: Betasol; Diabetofort; Herbaton†; Nefrobonisol; NeoFitolizyna†; Urosan†; Urosept; *Rus.*: Herbion Urological Drops (Гербион Урологические Капли); Sibectan (Сибектан); Urokam (Урокам); *S.Afr.*: Arnica Massage Oil; *Spain*: Diurinat; Genurat; *Switz.*: Dragees S pour les reins et la vessie; Impuls dragees pour la vessie et les reins; Nephrosolid; Sabrinin dragees pour les reins et la vessie; Tisane Diuretique; Tisane pour le coeur et la circulation; Tisane pour les reins et la vessie; Urinex; *UK*: Massage Balm with Calendula; *Ukr.*: Ambovit (Амбовит); Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Urochol (Урохол)†; Uronephron (Уронефрон).

Homoeopathic Preparations. *Canad.*: Homeodel 15†; Nixotinex; Urarthone†; *Cz.*: Galium; *Fr.*: Berberis Complexe No 83; Rheumadoron; Sclerocalcine; Urarthone; *Ger.*: Arnica comp/Apis†; Arnica/Betula comp; Arnica/Symphytum comp; K 1000; Levisticum S; Mandragora comp; Rheumodoron 102 A; *Switz.*: Rheumadoron; *UK*: Rheumadoron; Rheumadoron.

Black Catechu

Cutch; Акация-катеху (*Acacia catechu*).
CAS — 8001-76-1.
UNII — 55J167EEON.

NOTE. Distinguish from Catechu (p. 2472.3).

Pharmacopoeias. In *Chin.*

Profile

Black catechu is an extract from *Acacia catechu* (Leguminosae) that is used as an astringent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Herbadict; *India*: Arowash†; Kofiet; *Ukr.*: Travisil (Трависил).

Black Currant

Blackcurrant; Cassis; Grosella negra (casis); Rib. Nig.; Чёрная Смородина (*Ribes nigrum*).
ATC Herb — HR05YA5019 (Ribes nigrum fruit); HA07XA5011 (Ribes nigrum fruit).
UNII — 9Z55T40D11 (Ribes nigrum fruit); Z46FSZ2M25 (Ribes nigrum leaf).

Pharmacopoeias. *Br.* includes the fruit.

Eur. (see p. vii) includes the leaf.

BP 2014: (Black Currant). The fresh ripe fruits of *Ribes nigrum* with their pedicels and rachides. It has a strong, characteristic odour and a pleasantly acidic taste.

Profile

Black currant fruit is a source of vitamin C (p. 2110.3). It is used to prepare black currant syrup, which is used as a nutritional supplement and as a flavour.

Black currant leaf is included in herbal preparations for urinary, musculoskeletal, and gastrointestinal disorders. Black currant is reported to contain bioflavonoids and is also included in preparations for vascular disorders. It has also been used as a diuretic in folk medicine.

Black currant seed oil (below) is used as a source of gamolenic acid (see p. 2509.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Tiliv†.

Multi-ingredient Preparations. *Austria*: Amersan; *Cz.*: Amersan; *Fr.*: Arkophytum†; Arthritisane†; Arthroflorine†; Chondrosteo; Drainactil†; Expuryl; Glucarthroz; Hydracur; IgeE†; Mediflor Douleurs Articulaires no 2†; Mincifit†; Resource Rhubagil†; Rhumadol; Santane A_4†; Santane O1; Santane O1; Santane R_8†; Silibiol; Tisane Provencale no 6†; Urotisan†; Veinobiase; *Hung.*: Crategil; *Ital.*: Anaribes Plus; Flebotrofine; Gemiol Plus; Imoviral; Nepiros; Ribovir; *Pol.*: Melisal; Melissed; *S.Afr.*: Vitaforce Acerola C†; *Spain*: Exodren; Fitosvelt†; *Ukr.*: Vitokan (Витокан).

Pharmacopoeial Preparations
BP 2014: Black Currant Syrup.

Black Currant Seed Oil

Blackcurrant seed oil.
UNII — GKE1188837.

Profile

Black currant seed oil is derived from the seeds of *Ribes nigrum* (Grossulariaceae). It contains gamolenic acid (p. 2509.2) and is used similarly to evening primrose oil (p. 2502.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Solaire; *UK*: Skin Perfecting Oil; *Ukr.*: Perfectil Plus (Перфектил Плюс).

Black Haw

American Sloe; Nanny Bush; Stag Bush; Калина Сливолистная.
UNII — J411UTU0HN (Viburnum prunifolium bark).

Pharmacopoeias. In *Fr.*

Profile

The bark of black haw, *Viburnum prunifolium* (Adoxaceae) is claimed to have spasmolytic activity on uterine and other smooth muscle. It is included in herbal preparations for peripheral vascular disorders and menstrual disorders. The root bark is also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Aphloine P; Climaxol; Jouvence de l'Abbe Soury; Jouvence de l'Abbe Soury; Phlebosedol†; *Mon.*: Fluon.

Homoeopathic Preparations. *Fr.*: Aesculus Compose; Hamamelis Compose; Veino-Drainol†; *Ger.*: Pascofemin spasmo.

Black Nightshade

Hierba mora; Morelle Noire; Solano negro; Tomatillos del diablo; Паслён Чёрный.
UNII — 0FMD6WV47M (Solanum nigrum); XA101YXV55 (Solanum nigrum fruit); O4G5C1G3W5 (Solanum nigrum top).

Profile

Black nightshade is the leaves and flowering tops of the black or garden nightshade, *Solanum nigrum* (Solanaceae). It contains solanine and its allied alkaloids. Black nightshade is distributed throughout most of the world as a weed of cultivation. It appears to have little medicinal value although it has been used in some herbal products and in liniments, poultices, and decoctions for external application. Ingestion can cause typical antimuscarinic effects that may require treatment as described under Atropine, p. 1312.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Pol.*: Liv 52; *Rus.*: Bonjigar (Бонджигар); Dipana (Дипана); Liv 52 (Лив 52); Liv 52 (Лив 52); *Singapore*: Liv 52; Liv 52; *Ukr.*: Bonjigar (Бонджигар); Eve Care (Ив Кер)†; Liv 52 (Лив 52); Pilex (Пилекс).

Homoeopathic Preparations. *Canad.*: Arnica-Heel Comp†; Ateria-Heel†; *Fr.*: Poconeol no 71.

Blackthorn

Black Thorn; Épine noir; Prugnolo; Prunellier; Schlehe; Schwarzdorn; Sloe; Тёрн; Терновник.
ATC Herb — HA06AX5008 (Prunus spinosa flower).
UNII — 5342MY2M3P (Prunus spinosa); 53Y84VPS2W (Prunus spinosa flower bud); 181707E6S0 (Prunus spinosa flower water); 3ML84858X7 (Prunus spinosa fruit); UU3NL9WVML (Prunus spinosa wood).

Pharmacopoeias. *Br.* includes Prunus Spinosa Fruit for Homoeopathic Preparations.

BP 2014: (Prunus Spinosa Fruit for Homoeopathic Preparations). The fresh ripe fruit of *Prunus spinosa*.

Profile

The flowers of the blackthorn or sloe, *Prunus spinosa* (Rosaceae), are included in herbal preparations for constipation and urinary-tract disorders.

The fruit (sloes) are used for mild inflammation of oral and pharyngeal mucosa.

Culinary uses of sloes include preserves and as a flavour in alcoholic beverages.

Homoeopathy

Blackthorn is used in homoeopathic medicines under the following names: Prunus spin; Prunus spinosa; Prunus spinosa e summitatibus Rh; Prunus spinosa, Summitates Rh.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Schlehen Elixir†.

Multi-ingredient Preparations. *Ger.*: Schnupfencreme; Weleda Hauttonikum†; *S.Afr.*: Lotio Pruni Comp cum Cupro†; *Switz.*: Venadoron; Wala Baume nasal doux; Wala Baume nasal.

Homoeopathic Preparations. *Neth.*: Weleda Sleedoorn†; *UK*: Catarrh Cream.

Blue Cohosh

Caulófilo; Caulophyllum; Papoose Root; Squaw Root; Стеблелист Василистниковидный (*Caulophyllum thalictroides*).
UNII — 518LV969O6 (Caulophyllum thalictroides); JTJ6HH6YEH (Caulophyllum thalictroides root).

NOTE. Distinguish from Black Cohosh, which is Cimicifuga, p. 2478.1.

Uses and Administration

Blue cohosh, the rhizome and roots of *Caulophyllum thalictroides* (Berberidaceae), has uterotonic and antirheumatic properties. It is used for menstrual and other gynaecological disorders.

Homoeopathy

Blue cohosh has been used in homoeopathic medicines under the following names: Caulophyllum; Caulophyllum thalictroides; Caulph.

References.

1. Dugoua JJ, *et al.* Safety and efficacy of blue cohosh (Caulophyllum thalictroides) during pregnancy and lactation. *Can J Clin Pharmacol* 2008; **15**: e66–e73.

Adverse Effects

Effects on the cardiovascular system. Acute myocardial infarction associated with profound congestive heart failure and shock has been reported in a newborn infant whose mother ingested blue cohosh to promote uterine contractions.[1]

A case of cerebral infarct, resulting in motor seizures affecting the right arm, has also been reported[2] in a neonate born to a mother who used blue cohosh; screening revealed the presence of a cocaine metabolite, benzoylecgonine, in the herb, but it was unclear if this was due to contamination, or was a false-positive reaction caused by some other component.[3]

1. Jones TK, Lawson BM. Profound neonatal congestive heart failure caused by maternal consumption of blue cohosh herbal medication. *J Pediatr* 1998; **132**: 550–2.
2. Finkel RS, Zarlengo KM. Blue cohosh and perinatal stroke. *N Engl J Med* 2004; **351**: 302–3.
3. Finkel RS, Zarlengo KM. More on blue cohosh and perinatal stroke. *N Engl J Med* 2004; **351**: 2240–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Dyzco†.

Homoeopathic Preparations. *Austria*: Mastodynon; Pascofemin; *Canad.*: Comp-Drops 9†; Hylands PMS; Hylaprin; *Cz.*: Mastodynon; *Ger.*: Dysmenorrhoe-Gastreu S R75; Mastodynon; Naranofem†; Pascofemin spasmo; Pascofemin; *Neth.*: Mastodynon†; *Rus.*: Mastodynon (Мастодинон); *Thai.*: Mastodynon†; *Ukr.*: Mastodynon (Мастодинон).

Bog Myrtle

Sweet Gale; Восковница Обыкновенная (*Myrica gale*).

NOTE. Bog myrtle has also been used as a common name for *Menyanthes trifoliata* (see Menyanthes, p. 2554.2). Bayberry (see p. 2453.1) has also been used as a synonym for bog myrtle.

Profile

The essential oil obtained from bog myrtle, *Myrica gale* (Myricaceae), has been used as an insect repellent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: MozzyOff Cocktail.

Boldo

Boldi Folium; Boldo, feuille de; Boldo Folium; Boldo Leaves; Boldoblad; Boldólevél; Boldonlehti; Boldovníkový list; Hojas de boldo; Kvapijučių čilmedžių lapai; Liść boldo; Peumus; Больдо.
CAS — 476-70-0 (boldine); 1398-22-7 (boldoglucin).
ATC Herb — HA05AW5013 (Peumus boldus leaf); HG04BW5028 (Peumus boldus leaf).
UNII — Q4EWM09M3O.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes Boldo Leaf Dry Extract.

Fr. includes Boldine.

Ph. Eur. 8: (Boldo Leaf). The whole or fragmented dried leaf of *Peumus boldus*. It contains not more than 4% v/w of essential oil calculated with reference to the anhydrous drug. It contains not less than 0.1% of total alkaloids, expressed as boldine ($C_{19}H_{21}NO_4$ = 327.4), calculated with reference to the anhydrous drug. It has a characteristic odour especially when rubbed. Protect from light.

Profile

Boldo is employed in herbal medicine as a diuretic, for hepato-biliary disorders and for gastrointestinal disorders such as constipation. The alkaloid boldine is also used.

Homoeopathy

Boldo has been used in homoeopathic medicines under the following names: Peumus boldus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Hepatilon; Prinachol; *Canad.*: Cholarex; *Mex.*: Bliz†.

Multi-ingredient Preparations. *Arg.*: Alcachofa Plus; Bil 13; Boldina; Chofitol Plus; Digenat; Dioxicolagol; Drenocol; Fegalgina; Hepacur; Hepatalgina; Hepatalgina; Hepatodirectol; Incaico; Metiogen; Opobyl; Palatrobil; Radicura; Sabelin; Wunderbalsam; *Austral.*: Berberis Complex†; *Austria*: St Bonifatius-Tee†; *Braz.*: Colachofra; Ductoveran; Eparema; Figatil; Gotas Digestivas; Gotas Preciosas; Solvobil; *Canad.*: Hepaflor†; Hepaticol;

Hepatol; Herbaraphanus†; Phyto-Marinex; *Chile*: Hepabil; Nature Complex Reduct-Te; Reduc-Te; Te Laxante†; *Cz.*: The Salvat; *Fr.*: Afra†; Azema†; Bolcitol†; Boldoflorine; Boldoflorine; Boribel Tisane No 7†; Drainactil†; Elixir Spark†; Gastrotisane†; Hepaclem†; Hepatoflorine†; Jecopeptol†; Maalox Digestion Difficile; Mediflor Hepatique No 5; Mucinum a l'Extrait de Cascara; Opobyl†; Oxyboldine; Petites Pilules Carters†; Santane C_6†; Santane F_{10}†; Solution Stago Diluee; Tisane Garfield†; Tisane Hepatique de Hoerdt†; *Ger.*: Heumann Verdauungstee Solu-Lipar; *Ital.*: Amaro Medicinale; Boldina He; Caramelle alle Erbe Digestive; Cisteff; Colax†; Confetti Lassativi CM; Dis-Cinil Complex; Eparema-Levul; Eparema; Eupatol; Hepatos B12; Hepatos; Solvobil†; *Mex.*: Chofabol; Hepedren; Ifuchol; Peptochol; *Pol.*: Boldaloin; Boldovera; *Port.*: Mucinum; *Spain*: Nico Hepatocyn; Opobyl; Resolutivo Regium†; Solucion Schoum; *Swed.*: Cynaramin; *Switz.*: Boldocynara; Kernosan 24; Tisane hepatique et biliaire; *UK*: Adios; Aquella; Boldex; Digestisan; HealthAid Boldo-Plus; Milk Thistle Complex; Weight Loss Aid; *Venez.*: Cynascool; Natrossil.

Homoeopathic Preparations. *Canad.*: Cynara Complex†; Digestion; Formula FV 213; Hecocur†; *Chile*: Cynara Compuesta; Digherbal; *Fr.*: Aesculus Complexe No 103; L 114; Poconeol no 7; *Ger.*: EAP-61; *Neth.*: Apo-Hepat.

Boneset

Feverwort; Hierba de la fiebre; Thoroughwort; Посконник Прободённый (*Eupatorium perfoliatum*).
ATC Herb — HR05YA5006 (Eupatorium perfoliatum: *herb*).

NOTE. Boneset has also been used as a common name for *Symphytum officinale* (see Comfrey, p. 2484.2). Purple boneset is Gravel Root, p. 2522.1. The name Feverwort has also been used for *Centaurium erythraea* (see Centaury, p. 2473.2).

Profile

Boneset, the aerial parts of *Eupatorium perfoliatum* (Compositae), has diaphoretic and immunostimulant properties and has been used in the treatment of fever, influenza, the common cold, and other upper respiratory-tract disorders.

Homoeopathy

Boneset has been used in homoeopathic medicines under the following names: Eupatorium perfoliatum; Eupatorium perf; Eup. perf.

References.

1. Habtemariam S, Macpherson AM. Cytotoxicity and antibacterial activity of ethanol extract from leaves of a herbal drug, boneset (Eupatorium perfoliatum). *Phytother Res* 2000; 14: 575–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Flavons†; *Switz.*: Spagymun; *UK*: Catarrh Mixture.

Homoeopathic Preparations. *Austral.*: Childrens Cold and Flu Relief; Echine†; *Austria*: Ferrum Phosphoricum comp; Globuli gegen Grippe; Gripp Heel; Infludo; Nisylen†; toxi-loges; *Canad.*: C-Plus; Comp-Drops 5 Expectorant†; Complete Flu Care 4 Kids†; Echinacea Compositum; Formula INF; Hylands Flu; Hylands Formula P; Ikoplex 12†; Ivernax; L52 Cough & Cold; *Chile*: Ikoplex No 12; Influk; Similibus; *Cz.*: Gripp Heel; Lehnigrip†; Paragrippe; *Fr.*: Aconitum Compose†; Boripharm No 11†; grippe†; Infludo; L 52; Paragrippe; *Ger.*: Anovin; Broncho-Injektopas; Cefagrippin†; Contramutan; Echinacea comp; Eupatorium N Oligoplex; Ferrum phosphoricum comp; Gripp-Heel; Grippe-Gastreu S R6; Gripps; Immunorell; Infi-Echinacea; Infigripp; Infludo; Influvit; Jowidarmin; Nisylen; Pascoleucyn N; Pascoleucyn; phono Gripp; toxi-loges; toxi-loges; Wiedimmun N†; Wiedimmun; *Hung.*: Gripp-Heel; *Neth.*: Echilite; Echinacea comp; Febrilite; Gripp-Heel H; Grippe-Gastreu R6; Homeocare Revito; Infludo; Kind 0-6 Nisykind; Kruidvat Homeopathie Influ-complex†; Nisyleen; Paragrippe†; *Port.*: Paragrippe; *Rus.*: Berberis Comp (Барбарис Комп); Influcid (Инфлюцид); *S.Afr.*: Ferrum Phos Comp†; Gripp-Heel; Infludo†; *Switz.*: Gripp-Heel; Influaforce†; Infludo; *UK*: Infludo; *Ukr.*: Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Influcid (Инфлюцид); *USA*: Preferred Remedies Cold & Flu.

Borage

Borraja; Bourrache; Огуречник; Бораго.
ATC Herb — HJ01WB5005 (Borago officinalis: *herb*); *HM01AW5003* (Borago officinalis: *herb*); *HR05DB5003* (Borago officinalis: *herb*).
UNII — 7X2351OW1N (*borage flower*); *PB618V0K2W* (*borage leaf*).

Pharmacopoeias. *Fr.* includes monographs for flowers and flowering tops.

Profile

The aerial parts of borage *Borago officinalis* (Boraginaceae), have been used in herbal medicine as a demulcent and emollient. However, it contains pyrrolizidine alkaloids that may be toxic and internal use is not recommended.

Borage seeds are the source of borage oil (below), which is used as a source of gamolenic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Dexol.

Multi-ingredient Preparations. *Canad.*: Natraway Sport 1 & 2†; Natraway Sport 3†; *Chile*: Celltech; *Ital.*: Sclerovis H Plus; *Mex.*: Aveendix; *NZ*: Mr Nits.

Homoeopathic Preparations. *Chile*: TBR/X.

Borage Oil

Boraginis Oleum; Borago Officinalis Oleum; Borraja, aceite de; Bourrache, huile de; Brutnákový olej; Gurkörtolja; Purasruohoöljy; Starflower Oil; Vaistinių agurklių aliejus; Масло Бурачника.
UNII — F8XAG17555.

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

Ph. Eur. 8: (Borage (Starflower) Oil, Refined; Refined Borage Oil BP 2014). The fatty oil obtained from seeds of *Borago officinalis* by extraction and/or expression. It is then refined. A suitable antoxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.921. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers under an inert gas. Protect from light.

The BP 2014 gives Refined Starflower Oil as an approved synonym.

Profile

Borage oil is a source of essential fatty acids, mainly gamolenic acid (p. 2509.2). It is included in dietary supplements, often with fish oils or other sources of omega-3 fatty acids (see p. 1460.1).

Eczema. For the effects of borage oil on eczema, see under Gamolenic Acid, p. 2509.3.

Rheumatoid arthritis. For the use of borage oil as a source of gamolenic acid for the management of rheumatoid arthritis, see under Gamolenic Acid, p. 2510.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Tiliv L; *Fr.*: Omegaline; *Pol.*: Neoglandyna; *UK*: Floresse.

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; Cellasene†; La Edad De Oro; Ureadin Facial; *Braz.*: Borag; Gamaline-V; Liv-ten Vit; Primoris†; Votag O6; *Canad.*: Primanol Borage Oil†; *Chile*: Ureadin Facial Antiarrugas; Ureadin Facial; *Fr.*: Actyminé†; Alphalarm; Alpharegul Femme; Alpharegul Homme; Androlistica; Effadiane relipidantes; Elteans; Feminabiane Cycle Feminin; Feminabiane Meno'Confort; GliSODine Solaire; Menolistica; Omegaline Solaire; Phytophanere†; Phytosolaire†; Topialyse Sensitive; Topialyse Sensitive; Topialyse Sensitive; Topialyse; *Hung.*: Fumago; Klimin; Memolife; Obesmin; *Ital.*: Biophase Complex†; LCP; Secril; Spm-OK; Topialyse; *Port.*: Antiestrias; Bioclin Sebo Care; Hidratante VV; Nutraisdin; Nutraisdin; Rilastil Anti-Oxidante; Rilastil Dermo Solar; Ureadin Facial; *Singapore*: Androlistica; Manhae; Seven Seas EPO Plus Starflower Oil; *UK*: Arheumacare; Super Antioxidant Plus; *Ukr.*: Wellwoman (Веллумен).

Borax

Booraksi; Boraksas; Borato de sodio decahidratado; Bórax; Disodium Tetraborate; Disodu tetraboran; E285; Heptaoxotetraborato de sodio decahidratado; Natrii Tetraboras; Natrii Tetraboras Decahydricus; Natrium Boricum; Natriumtetraborat; Nátrium-tetraborát; Purified Borax; Sodium Biborate; Sodium Borate; Sodium Pyroborate; Sodium Tetraborate; Sodu tetraboran; Tetraborato de sodio; Tetraboritan sodný dekahydrát; Бура; Боракс.
$Na_2B_4O_7,10H_2O$=381.4
CAS — 1330-43-4 (anhydrous borax); 61028-24-8 (anhydrous borax); 1303-96-4 (borax decahydrate).
ATC — S01AX07.
ATC Vet — QS01AX07.
UNII — 91MBZ8H3QO (sodium borate decahydrate); 8191EN8ZMD (anhydrous sodium borate).

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

Ph. Eur. 8: (Borax). Colourless crystals or crystalline masses, or white or almost white, crystalline powder. It effloresces. Soluble in water; very soluble in boiling water; freely soluble in glycerol. A 4% solution in water has a pH of 9.0 to 9.6.

The BP 2014 gives Sodium Borate and Sodium Tetraborate as official synonyms.

USNF 31: (Sodium Borate). Odourless transparent colourless crystals or white crystalline powder. Its solutions are alkaline to phenolphthalein. It effloresces in warm dry air. Soluble 1 in 16 of water, 1 in 1 of boiling water, and 1 in 1 of glycerol; insoluble in alcohol. Store in airtight containers.

Boric Acid

Acide borique; Ácido bórico; Acidum boricum; Boorihappo; Boracic Acid; Borato rugštis; Borsäure; Bórsav; Borsyra; E284; Kwas borowy; Kyselina boritá; Orthoboric Acid; Sal Sedativa de Homberg; Борная Кислота.
H_3BO_3=61.83
CAS — 10043-35-3.
ATC — S02AA03.
ATC Vet — QS02AA03.
UNII — R57ZHV85D4.

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

Ph. Eur. 8: (Boric Acid). Colourless shiny plates greasy to the touch, or white or almost white crystals, or white or almost white crystalline powder. Soluble in water and in alcohol; freely soluble in boiling water and in glycerol (85%). A 3.3% solution in water has a pH of 3.8 to 4.8.

USNF 31: (Boric Acid). Odourless, colourless, somewhat pearly lustrous scales, or crystals, or white powder, slightly unctuous to the touch. Soluble 1 in 18 of water, 1 in 4 of boiling water, 1 in 18 of alcohol, 1 in 6 of boiling alcohol, and 1 in 4 of glycerol.

Stability. Boric acid volatilises in steam. It forms a complex with glycerol which is a stronger acid than boric acid.

Uses and Administration

Boric acid possesses weak bacteriostatic and fungistatic properties; it has generally been superseded by more effective and less toxic disinfectants. It is used as a pesticide against ants and cockroaches.

Boric acid is used, usually with borax, as a buffer and antimicrobial in eye drops, and was formerly used as a soluble lubricant in solution-tablets. It is also used as a preservative for urine samples. Boric acid and borax are not used internally.

In the UK, the use of boric acid in cosmetics and toiletries is restricted (see Adverse Effects, p. 2460.1).

Borax is used similarly to boric acid and has also been used externally as a mild astringent and as an emulsifier in creams. Preparations of borax in glycerol or in honey (Borax Glycerin; Honey of Borax) were formerly used as paints for the throat, tongue, and mouth, but should not be used because of the risk of toxicity.

Other salts of boric acid, including potassium and zinc salts, have been used.

Homoeopathy

Boric acid has been used in homoeopathic medicines under the following names: Acidum boricum; Acidum Boracicum; Ac. boric.; Boricum acidum; Boricum ac.

Borax has been used in homoeopathic medicines under the following names: Natrium tetraboracicum.

Urine preservation. Boric acid in concentrations of about 2% may be a suitable preservative for urine samples in transit requiring bacteriological examination.[1,2] However, overnight storage of specimens preserved with boric acid may significantly alter culture results.[3]

1. Porter IA, Brodie J. Boric acid preservation of urine samples. *BMJ* 1969; 2: 353–5.
2. Lum KT, Meers PD. Boric acid converts urine into an effective bacteriostatic transport medium. *J Infect* 1989; 18: 51–8.
3. Gillespie T, *et al.* The effect of specimen processing delay on borate urine preservation. *J Clin Pathol* 1999; 52: 95–8.

Vaginitis. Vaginal candidiasis (p. 564.1) caused by *Candida glabrata* and other non-*albicans* species frequently responds to topical boric acid.[1,2] Satisfactory clinical and mycological responses to topical boric acid were reported in 2 patients with *Candida glabrata* vaginitis who had not responded to repeated courses of azole antifungals.[3] Treatment with boric acid effected clinical and mycological cure in 4 of 6 patients with refractory vaginitis caused by *C. krusei*.[4] Long-term boric acid treatment showed promise in the treatment and prevention of relapses of vulvovaginal candidiasis, but its efficacy ended when treatment was stopped.[5] Similarly, a study in diabetic women[6] found that although initial response to a 14-day course of topical boric acid was better than with fluconazole, relapse was common over the subsequent 3 months.

1. Sobel JD, Chaim W. Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. *Clin Infect Dis* 1997; 24: 649–52.

2. Pappas PG, *et al.* Infectious Diseases Society of America. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; 38: 161–89. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/380796 (accessed 24/07/08)
3. Redondo-Lopez V, *et al.* Torulopsis glabrata vaginitis: clinical aspects and susceptibility of antifungal agents. *Obstet Gynecol* 1990; 76: 651–5.
4. Singh S, *et al.* Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. *Clin Infect Dis* 2002; 35: 1066–70.
5. Guaschino S, *et al.* Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol* 2001; 184: 598–602.
6. Ray D, *et al.* Prolonged (3-month) mycological cure rate after boric acid suppositories in diabetic women with vulvovaginal candidiasis. *J Infect* 2007; 55: 374–7.

Adverse Effects, Treatment, and Precautions

The main symptoms of acute boric acid poisoning are vomiting and diarrhoea, abdominal pain, an erythematous rash involving both skin and mucous membranes, followed by desquamation, and stimulation or depression of the CNS. There may be convulsions and hyperpyrexia. There may also be renal tubular damage. Abnormal liver function and jaundice have been reported rarely. Death, resulting from circulatory collapse and shock, may occur within several days.

The slow excretion of boric acid can lead to cumulative toxicity during repeated use. Symptoms of chronic intoxication include anorexia, gastrointestinal disturbances, debility, confusion, dermatitis, menstrual disorders, anaemia, convulsions, and alopecia.

Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid or after the application of boric acid powder to abraded skin.

In the UK the use of boric acid, borates, and tetraborates in cosmetics is controlled: the concentration is limited to 5% in talcs, to 0.1% in products for oral hygiene, and to 3% in other cosmetic products; tetraborates are limited to 8% in hair waving products and 18% in bath products. Such cosmetic products should not be used in children under 3 years of age; preparations used for oral hygiene should not be swallowed; and topical preparations containing greater than the equivalent of 1.5% of boric acid should not be applied to peeling or irritated skin.

Deaths have resulted from absorption after lavage of body cavities with solutions of boric acid, and this practice is no longer recommended.

Inhaled boric acid and borax are pulmonary irritants.

Treatment of poisoning is symptomatic. The stomach should be emptied if the patient presents within 1 hour of ingesting a large amount of boric acid; activated charcoal is not effective. Haemodialysis may be of value in severe cases.

In Great Britain pharmacists have been advised not to sell boric acid as such for use as a dusting powder (see also above). Pharmacists have also been advised not to supply Borax Glycerin or Honey of Borax, even with an appropriate warning, because of the hazards associated with the use of these preparations in infants.

Pharmacokinetics

Boric acid is absorbed from the gastrointestinal tract, from damaged skin, from wounds, and from mucous membranes. It does not readily penetrate intact skin. About 50% of the amount absorbed is excreted in the urine within 24 hours and most of the remainder is excreted within 96 hours of ingestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Eye Wash; ***China***: Yin Tai (殷泰); ***Fr.***: Dacryum; Hydralin Classic; ***Ital.***: AB 300; ***Mon.***: Steridose; ***Pol.***: Aphtin; Borasol; Gemiderma; ***Thai.***: Glycerin of Borax; ***Turk.***: Bibora; ***Venez.***: Sax.

Multi-ingredient Preparations. ***Arg.***: Anusol-HC; Anusol†; Baby-Tex; Bentophyto; Calcusan Bebe; Cutidermin Bebe Polvo†; Fil Olor; Fungocop; Gineseptina; Griseoplus; Hipoglos Cicatrizante; Hipoglos con Hidrocortisona; Irigal; Lemil; Phylarm; Prurisedan; Sebulex; ***Austral.***: Joint Formula Advanced; ***Austria***: Coldophthal; Ophtaguttal; ***Belg.***: Alcasol; Boradrine†; Borostyrol; Sedemol; Sulfa-Sedemol; ***Braz.***: Cloraseptic; Colpagex-N†; Dinill; Gynax-N; Higicler; Hipodermon; Lucretin; Malvona; Oturga; Po Antisseptico†; Pomaderme; Vagitrin-N; Visiplex; ***Canad.***: Refresh Ultra; ***Chile***: Dexagin; Frescansol; Hipoglos; Pediaderm; Perfungol; ***China***: Bi Zhi Ke (比之可); ***Cz.***: Caltrate Plus; Herbadent; Ophtal; Ophthalmo-Septonex; Pityol; ***Fin.***: Otiborin; ***Fr.***: Borostyrol; Dacryoboraline†; Dacryoserum; Dacudoses; Eau Precieuse†; Homeoplasmine; Hydralin Classic; Ophtalmine†; Paps†; PhyLarm; Sophtal; Supro; ***Gr.***: Oulogram; Septobore; Vaseline Borique; ***Hong Kong***: Eye Glo Plus; Eye Glo Regular; Eye Wash; Gly Thymol; Hydralin; ***India***: Andre; Boroswift; Borozin; Coldtaur; Decomic; Dermal; Distone; Feel Chill†; Fista; Gencart; Geocal; Healing Dust; I-Top; Irimist; Itchasia; Mil; Moisol; Naflin; New Eye Lotion†; NFBor; Ocuclear; Osmotic-6; Proto-Boric†; ***Indon.***: Skintex†; Verile; ***Irl.***: Phytex†; ***Israel***: Claritone; Gargol; ***Ital.***: Bergacid†; Boma; Fotofil; Fucsina Fenica; ***Mex.***: Clarex; Forcremol; Hipoglos; Lav Ofteno; Lowila; Oftaboril; Tokolirio; ***Mon.***: Borociarine†; Glyco-Thymoline; ***Philipp.***: Soothing Eye Wash; United Home Burn Ointment; ***Pol.***: Acifungin; Afronis; Antypot; Dentosept A; Gargarin; Hemorectal; Neo-Tormentil; Tormentile Forte; Tormentiol; ***Rus.***: Calcemin (Кальцемин); Combutec-2 (Комбутек-2); Contraceptin T (Контрацептин Т); Fucaseptol (Фукасептол); Fucorcin (Фукорцин); Linin (Линин); Lysoplac (Лизоплак)†; Oftalmol (Офтальмол); Olasol (Олазоль); Osarbon (Осарбон); Ottoslavin (Оттославин); Teimurov (Теймурова); ***S.Afr.***: Anugesic†; Caloplast†; Prep†; Universal Eye Drops†; Vagarsol; ***Singapore***: Castellani's Paint; Eye Mo; ***Spain***: Banoftal†; Cloram Hemidex†; Coliriocilina Adren Astr†; Dermomycose Liquido; Fungusol; Milrosina; Natusan; Oftalmol Ocular; Vaselina Boricada†; Zolina; ***Thai.***: Eye Mo; Eye-Gene Soft; Eye-Gene; Mano; Opplin; Opsil; Optal; Optic; Quinradon-N†; Visotone; Visotone; ***Turk.***: Dermikolin; Undo-Talk; ***UK***: Oxy Clean Facial Scrub; Phytex; ***Ukr.***: Calcemin Advance (Кальцемин Адванс); Pilex (Пилекс); Vitrum Osteomag (Витрум Остеомаг); ***USA***: BFI; Castaderm; Collyrium for Fresh Eyes†; Columbia Antiseptic Powder; Ear-Dry; Paladin; Palomar E; Phylorinol; RA Lotion; Saratoga; Seale's Lotion; Star-Otic; Trimo-San; ***Venez.***: Ademina; Borocanfor; Borogin; Micofeet; Sebaxyl.

Homoeopathic Preparations. ***Austria***: Otodolor; Otovowen; ***Canad.***: Bioactiv H†; Cold Sores & Fever Blisters; Homeoplasmine; Hylavir FB†; Kids' Teething; ***Chile***: Bioactiv H; ***Fr.***: Aftosium; Boripharm No 10†; Gastro-Drainol†; Homeoaftyl; Poconeol no 82†; Staphysagria Complexe No 92†; ***Ger.***: Hewesoor N†; Otovowen; ***Rus.***: Avia-Mor (Авиа-Море); ***Switz.***: Regenaplex Nr 28b; ***USA***: Succus Cineraria Maritima†.

Pharmacopoeial Preparations
BP 2014: Kaolin Poultice;
BPC 1973: Magenta Paint; Surgical Chlorinated Soda Solution;
USP 36: Rose Water Ointment.

Borneol

Baros Camphor; Bhimsaim Camphor; Borneo Camphor; Borneokampfer; Bornyl Alcohol; Camphol; Dryobalanops Camphor; Malayan Camphor; Sumatra Camphor; Борнеол.
endo-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol.
$C_{10}H_{18}O$=154.3
CAS — 507-70-0.
UNII — M89NIB437X.

Pharmacopoeias. In *Chin* as synthetic borneol (Borneolum Syntheticum).

Profile

Borneol is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Rowatinex; ***Austria***: Rowachol; Rowatinex; ***Chile***: Rowatinex; ***Cz.***: Rowachol; Rowatinex; ***Ger.***: Rowachol; Rowatinex; ***Hong Kong***: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; ***Hung.***: Rowachol; Rowatinex; ***Indon.***: Penfri; Stobled; ***Irl.***: Rowachol; Rowatinex; ***Israel***: Rowachol; Rowatinex; ***Malaysia***: Rowachol; Rowatinex; ***Mex.***: Cholex; ***Philipp.***: Mentopas; Rowachol; Rowatinex; ***Pol.***: Rowachol; Rowatinex; Terpichol; ***Rus.***: Rowatinex (Роватинекс); Wantong Artiplas (Ваньтун Артиплас); ***Spain***: Rowachol; Rowanefrin; ***Thai.***: Rowachol; Rowatinex; ***UK***: Rowachol; ***Ukr.***: Bezornil (Безорнил); Koronatera (Коронатера); ***Venez.***: Rowachol; Rowatinex.

Bornyl Acetate *(USAN)*

Borneol Acetate; Bornilo, acetato de; Bornylu octan; Борнилацетат.
1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol acetate.
$C_{12}H_{20}O_2$=196.3
CAS — 76-49-3 (bornyl acetate); 125-12-2 (isobornyl acetate).
UNII — 213431586X.

Profile

Bornyl acetate is a constituent of some essential oils. It has been used in aromatic preparations in the treatment of coughs, other respiratory-tract disorders, and musculoskeletal and joint disorders. Isobornyl acetate has been used similarly; it has also been used in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Jabonacid; ***Chile***: Expanden; ***Ger.***: Rheubalmin Bad; ***Hung.***: Nozi; ***Switz.***: Perskindol Classic.

Bromelains *(BAN, USAN, rINN)* ⊗

Bromelaiinit; Bromelaina; Bromelaina; Bromelainer; Bromelainy; Bromélaïones; Bromelins; EC 3.4.22.33; Plant Protease Concentrate; Бромелаины.
CAS — 9001-00-7.
ATC — B06AA11.
ATC Vet — QB06AA11.
ATC Herb — HA09AA5001 (Ananas comosus: extract); HD03WX5002 (Ananas comosus: extract).
UNII — U182GP2CF3 (bromelains); F0ZCA6O9QT (fruit bromelain).

Units

One Rorer unit of protease activity has been defined as that amount of enzyme which hydrolyses a standardised casein substrate at pH 7 and 25 degrees so as to cause an increase in absorbance of 0.00001 per minute at 280 nm. FIP units are also defined in terms of rate of hydrolysis of bromelain activity of a casein preparation under standard conditions.

Activity has also been described in terms of milk-clotting units.

Uses and Administration

Bromelains are a concentrate of proteolytic enzymes derived from the pineapple plant, *Ananas comosus* (*A. sativus*) (Bromeliaceae). They are used as an adjunct in the treatment of soft-tissue inflammation and oedema associated with trauma and surgery. Bromelains have also been given as an aid to digestion, and used in the treatment of partial deep dermal and full thickness burns.

References.

1. Kane S, Goldberg MJ. Use of bromelain for mild ulcerative colitis. *Ann Intern Med* 2000; 132: 680.
2. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci* 2001; 58: 1234–45.

Adverse Effects

Bromelains may cause nausea, vomiting, and diarrhoea. Metrorrhagia and menorrhagia have occasionally occurred. Hypersensitivity reactions have been reported and have included skin reactions and asthma.

Effects on the respiratory system. Bronchial asthma occurred in 2 patients after exposure to bromelains.[1] Of 6 workers sensitised to papain, 5 had positive skin tests to bromelains and 2 of them also had immediate asthmatic reactions after bronchial challenge with bromelains.[2]

1. Galleguillos F, Rodriguez JC. Asthma caused by bromelin inhalation. *Clin Allergy* 1978; 8: 21–4.
2. Baur X, Fruhmann G. Allergic reactions, including asthma, to the pineapple protease bromelain following occupational exposure. *Clin Allergy* 1979; 9: 443–50.

Precautions

Bromelains should be given with care to patients with coagulation disorders or with severe hepatic or renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Ananase Forte; ***Fr.***: Extranase; ***Ger.***: Dontisanin†; Mucozym†; Phlogenzym mono; Proteozym; Traumanase; Wobenzym mono†; ***Hong Kong***: Internase; ***Ital.***: Ananase; ***Neth.***: NexoBrid; ***Port.***: Ananase; ***Switz.***: Traumanase; ***Venez.***: Ananase.

Multi-ingredient Preparations. ***Arg.***: Varicofem; ***Austral.***: Bio-Disc†; Digest Aid; Digestaid; Herbidisc; Tresos B PluSe; Vegie Digestaid; ***Austria***: Phlogenzym; Rutozym; Traumazym; Wobenzym; ***Braz.***: Monocetin†; Plasil Enzimatico; Sintozima†; ***Canad.***: Mega Zyme†; Multi Enzyme†; Multi-Zyme†; Wobenzym; ***Cz.***: Phlogenzym; Wobenzym; ***Ger.***: Phlogenzym†; Wobenzym plus; ***Hung.***: Phlogenzym; Salus Multipretten; ***India***: Baknil; Bree-C; Disperzyme; Enractin; Merckenzyme†; ***Indon.***: Benozym; Elsazym; ***Ital.***: Algorex; Flogofort; Flogovis IdroGel; Flogovis; Inflamase IdroGel; Inflamase; Flogovis†; Signum; ***Jpn***: Kimotab†; ***Malaysia***: Enzyme Digest; ***Mex.***: Phlogenzym; Plasil Enzimatico; Wobenzym; ***Philipp.***: Lungcaire Plus; ***Rus.***: Phlogenzym (Флогэнзим); Wobenzym (Вобэнзим); ***Singapore***: Essentials†; ***Turk.***: Ultimate; ***UK***: BackOsamine; Enzyme Digest; ***Ukr.***: Ektis (Эктис); Phlogenzym (Флогэнзим); Wobenzym (Вобэнзим); ***USA***: Bio-Zyme; ***Venez.***: Nutizym Compositum; Phlogenzym; Wobenzym N.

Bromides

Bromuros; Бромиды.
ATC — N05CM11.
ATC Vet — QN05CM11.

Ammonium Bromide

Ammon. Brom.; Ammonii Bromidum; Ammonium Bromatum; Ammonium, bromure d'; Ammónium-bromid; Ammoniumbromid; Ammoniumbromidi; Amonio bromidas; Amonowy bromek; Brometo de Amônio; Bromid amonný; Бромид Аммония; Бромистый Аммоний.
NH_4Br=97.94
CAS — 12124-97-9.
UNII — R0JB3224WS.

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

Ph. Eur. 8: (Ammonium Bromide). A white or almost white, hygroscopic crystalline powder or colourless crystals. It becomes yellow when exposed to light or air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

Potassium Bromide

Brometo de Potássio; Bromid draselný; Bromure de Potassium; Kalii bromidum; Kalio bromidas; Kalium Bromatum; Kaliumbromid; Kálium-bromid; Kaliumbromidi; Pot. Brom.; Potassii Bromidum; Potassium, bromure de; Potasu bromek; Бромистый Калий.
KBr=119.0
CAS — 7758-02-3.
UNII — OSD78555ZM.

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

Ph. Eur. 8: (Potassium Bromide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

USP 36: (Potassium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

Sodium Bromide

Brometo de Sódio; Bromid sodný; Bromure de Sodium; Natrii bromidum; Natrio bromidas; Natrium Bromatum; Natriumbromid; Nátrium-bromid; Natriumbromidi; Sod. Brom.; Sodii Bromidum; Sodium, bromure de; Sodu bromek; Бромистый Натрий.
NaBr=102.9
CAS — 7647-15-6.
UNII — LC1V549NOM.

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

Ph. Eur. 8: (Sodium Bromide). A slightly hygroscopic, white or almost white, granular powder, or small, colourless, transparent, or opaque crystals. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 36: (Sodium Bromide). A white crystalline powder or colourless, cubical crystals. Freely soluble in water; soluble in alcohol.

Uses and Administration

Bromides depress the CNS. Calcium, potassium, and sodium bromide have been used as sedatives and anticonvulsants, but have generally been replaced by more effective, less toxic drugs. Ammonium and strontium bromide have been used similarly, as have bromoform and dilute hydrobromic acid. Bromides have also been used in multi-ingredient preparations for the treatment of coughs.

Homoeopathy

Hydrobromic acid and various bromides have been used in homoeopathic medicines under the following names:

- Hydrobromic acid: Hydr. ac.
- Ammonium bromide: Ammonium bromatum; Ammonium bromidum; Amm. brom.; Ammon brom
- Arsenic bromide: Arsenicum bromatum; Arsenicum brom; Ars. brom.
- Cadmium bromide: Cadmium bromatum; Cadmium brom; Cad. brom.
- Calcium bromide: Calcarea bromata; Calc. bro.
- Ferrous bromide: Ferrum bromatum; Ferrum brom; Fer. brom.
- Potassium bromide: Kalium bromatum; Kali bromatum; Kali brom;Kali. br.
- Sodium bromide: Natrum bromatum; Nat. brom.
- Radium bromide: Radium bromatum; Radium brom; Rad. br.
- Zinc bromide: Zincum bromatum; Zinc brom; Zinc. br.

Adverse Effects and Precautions

During prolonged exposure bromide accumulation may occur giving rise to bromide intoxication or bromism. Symptoms include nausea and vomiting, anorexia, confusion, behavioural disturbances, slurred speech, memory impairment, drowsiness, irritability, ataxia, tremors, hallucinations, mania, delirium, psychoses, stupor, coma, and other manifestations of CNS depression. Rashes of various types may occur and toxic epidermal necrolysis has been reported. Death after acute poisoning appears to be rare as vomiting follows the ingestion of large doses.

There have been reports of neonatal bromide intoxication and growth defects associated with maternal bromide ingestion during pregnancy.

Breast feeding. The American Academy of Pediatrics[1] considers that intake of bromides is usually compatible with breast feeding, although rashes, weakness, and absence of crying have been reported in the infant after maternal intake. Exposure to bromides in photographic laboratories may also result in potential absorption and transfer into breast milk.

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://pediatrics.aappublications.org/cgi/content/full/108/3/776 (accessed 22/07/08)

Treatment of Adverse Effects

In acute poisoning, the stomach should be emptied (if emesis has not already occurred), and sodium chloride should be given by intravenous infusion. Glucose may also be used and furosemide may be given to aid diuresis.

In chronic poisoning, bromides are stopped and sodium chloride is given intravenously or orally with adequate amounts of fluid. Ammonium chloride has been given but is no longer recommended as it may precipitate metabolic acidosis. Diuretics are of value. In severe cases of bromide intoxication, or when the usual treatments cannot be used, haemodialysis may be of benefit.

Pharmacokinetics

Bromides are readily absorbed from the gastrointestinal tract. They displace chloride in extracellular body fluids and have a half-life in the body of about 12 days. They may be distributed into breast milk and cross the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Dibro-Be Mono.

Multi-ingredient Preparations. *Braz.*: Frenotosse; *Chile*: Gruben; Pectokast; Ramistos; *Fr.*: Galirene†; Sedatif Tiber†; Sel D; *Ger.*: Adelheid-Jodquelle, Tolzer; *Hung.*: Yam; *India*: Gynedol; *Indon.*: Thymcal; *Ital.*: Fertomcidina-U; *Pol.*: Sal Ems Factitium; *Rus.*: Amtersol (Амтерсол); Bromenval (Бромевал); Cardiovalen (Кардиовален); Pertussin (Пертуссин); Valocormid (Валокормид).

Homoeopathic Preparations. *Austria*: Exangina†; Nervoheel; Sensicare; Tonsillopas; Valerianaheel; *Canad.*: Acne; Nervita; Quietude; *Cz.*: Sedalia; Spascupreel S†; *Fr.*: Abbe Chaupitre no 1†; Abbe Chaupitre no 91†; Quietude; *Ger.*: Drufusan N†; Liquidorm N; Mato; Mullersche Tabletten; Roth's RKT Tropfen; Rytesthin; Sedacalman; Sedaphin†; Spascupreel; Tonsillopas; *Hung.*: Nervoheel; Spascupreel; *Neth.*: Gynaelite; Nervoheel; Quietude†; *Rus.*: Psorilom (Псорилом); *Switz.*: Nelsons Noctura†; Nervoheel; Quietude; *UK*: Noctura; *USA*: Eczemol.

Bromine

Brom; Brome; Bromium; Bromo; Bromum; Бром.
Br_2=159.808
CAS — 7726-95-6.
UNII — SBV4XY874G.

Description. Bromine is a dark reddish-brown, heavy, mobile liquid that gives off intensely irritating brown fumes.

Uses and Administration

Bromine is widely used in industry. It was formerly used, in the form of an adduct with a quaternary ammonium compound, in the treatment of plantar warts.

Adverse Effects

Bromine is intensely irritating and corrosive to eyes and mucous membranes; it may cause severe gastro-enteritis if swallowed. Contact with the skin can produce severe burns, and inhalation of the vapour causes violent irritation of the respiratory tract and pulmonary oedema.

Treatment of Adverse Effects

Milk or water should be given as soon as possible after ingestion of bromine. Gastric lavage, activated charcoal, ipecacuanha, and neutralisation are not recommended. If bromine vapour has been inhaled, oxygen should be given and assisted ventilation may be necessary. The use of prophylactic corticosteroids for laryngeal and pulmonary oedema is controversial. Splashes on the skin and eyes should be immediately washed off; washing with copious amounts of water should continue for at least 15 minutes after skin exposure, and with sodium chloride 0.9% for at least 30 minutes after eye exposure.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Roxalia; *Cz.*: Homeogene 9; *Fr.*: Homeogene 9; *Hung.*: Homeogene 9; *Neth.*: Homeogene 9†; *Port.*: Homeogene 9; *Rus.*: Valeriana-Plus (Валериана-Плюс); *Switz.*: Homeogene 9.

Bryonia

Brionia; Bryony; Nueza; Переступень; Брония.
ATC Herb — HA06AB5004 (Bryonia dioica: root).
UNII — T7J046YI2B.

Profile

Bryonia, the root of *Bryonia alba* or *B. dioica* (Cucurbitaceae), is an ingredient of preparations that have been used in respiratory-tract infections and inflammatory disorders. Toxic symptoms and fatalities have been reported after ingestion of the berries.

Homoeopathy

Bryonia has been used in homoeopathic medicines under the following names: Bryonia cretica; Bryonia e radice; Bry. cre.; Bryonia alba; Bry. alba.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Homeoplasmine; *Ger.*: Schnupfencreme; *Mex.*: Reudol; *Port.*: Stodal.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Arthritis Relief; Childrens Cold and Flu Relief; Childrens Cough Relief; Colic Relief; Joint & Muscle Oral Spray†; Respatona Dry Cough & Nasal Congestion; Respatona Sore Throat; Sports Ice Joint & Muscle; *Austria*: Aconitum Med Complex; Aflubin; Ferrum Phosphoricum comp; Infludo; Nisylen†; Pneumodoron Nr 1; Rhus Med Complex; Sulfur Med Complex; Tonsan akut; toxiloges; *Canad.*: Aches & Pains; Arnica-Heel Comp†; Arthflex; Artis-Heel†; Bronkeel†; Bryaconeel†; Calnor†; Comp-Drops 3 Bowel Support†; Comp-Drops 5 Expectorant†; Complete Flu Care 4 Kids†; Cou Complex†; Echinacea Compositum; Fibromyalgie; Formula DM 210†; Formula INF; Homeo-Form C†; Homeo-Form G†; Homeo-Form ME†; Homeoplasmine; Homeovox; Hylagesic APF; Hylands Cough; Hylands Flu; Hylands Formula F; Ivemax; Kids Cough & Cold Phytux; Menopause L122; Menopause; Phytotux H; Roxalia; Spigelon†; Stodal; Toxex; *Chile*: Bioactiv V; Influk; Similibus; *Cz.*: Bronchalis-Heel; Gripp Heel; Homeogene 9; Homeovox; Lehnigrip†; Stodal; *Fr.*: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 25†; Abbe Chaupitre no 6; Abbe Chaupitre no 88†; Aconitum Compose†; Aloe Compose; Arthro-Drainol; Baudry; Boripharm No 23; Bryonia Opodeldoch; Cholesterolum Complexe No 112†; Homeogene 14†; Homeogene 9; Homeogrippe†; Homeovox; Infludo; Ipeca Compose; Kalium Muriaticum Complexe No 41†; L 107; Lachesis Complexe No 122; Nux Vomica Complexe No 49; Nux Vomica Compose; Pates Pectorales; Pulmo-Drainol†; Pulsatilla Complexe No 60†; Ranunculus Complexe No 79; Stodal; Stodal; *Ger.*: Arthrokatt; Bronchi-Do; Bronchiselect; Bryorheum N; Capillaron Vertigo; Echinacin akut; Entzundungstropfen; Eupatorium N Oligoplex; Ferrum phosphoricum comp; G1-Injektopas; Gelenk Albin; Genu-cyl L Ho-Len-Complex; Gripp-Heel; Grippe-Gastreu S R6; Gripps; Hevertotox; Hewerheum N†; Infekt 1-Injektopas N; Infi-Echinacea; Infigripp; Infludo; Jutussin; Lowe-Komplex Nr 6; Mato; Nisylen; Nux Vomica N Oligoplex; Pascoe-Agil HOM; Pascoleucyn; Pascoleucyn; Pneumodoron 1; Pulmo-cyl Ho-Len-Complex; Pyrogenium; Rheucostan R; Rheuma-Hevert; Rheuma-Hevert; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Rheumodoron 1; Rhus toxicodendron N Oligoplex; Schworotox; toxi-loges; Toxiselect; Traumakatt; Tussistin S; Tussistin; *Hung.*: Aflubin; Gripp-Heel; Homeogene 9; Homeovox; Spigelon; Stodal; *Neth.*: Bronchalis; Echinacea comp; *Port.*: Homeogene 9; Homeoplasmine†; Homeovox; *Rus.*: Aflubin (Афлубин); Belladonna-Plus (Белладонна-Плюс); Briacon (Бриакон); Capsicum-Plus (Капсикум-Плюс); Homeovox (Гомеовокс); Influcid (Инфлюцид); Sambucus-Plus (Самбукус-Плюс); Stodal (Стодаль); Tonsan-Akut (Тонзан-акут); *S.Afr.*: Ferrum Phos Comp†; Gripp-Heel; Infludo†; Pneumodoron 1†; *Switz.*: Infludo; metaossylen N; Regenaplex Nr 38b; Regenaplex Nr 41a; Regenaplex Nr. 35b; Regenaplex Nr. 50b; TussEx; *UK*: Sootha; *Ukr.*: Aflubin (Афлубин); Homeovox (Гомеовокс); Homvio-Reuman (Хомвио-Ревман); Influcid (Инфлюцид); Stodal (Стодаль).

Buchu

Barosma; Bucco; Buchú; Buchu Leaves; Diosma; Folia Bucco; Hojas de buchú; Бучу.
CAS — 68650-46-4 (buchu leaf oil).

ATC Herb — HG04BW5002 (Agathosma betulina: *leaf*); *HJ01WB5001* (Agathosma betulina: *leaf*).
UNII — 369DDH39Z0 (Agathosma betulina *leaf*); *KO5935A04V* (*buchu leaves extract*).

Pharmacopoeias. In *Fr.*, which allows the dried leaves of *Agathosma betulina* (short or round buchu), *A. crenulata* (oval buchu), and *A. serratifolia* (long buchu).

Profile

Buchu, the dried leaves of 'short' or 'round' buchu, *Agathosma betulina* (*Barosma betulina*) (Rutaceae), is a weak diuretic and urinary antiseptic that has been used in multi-ingredient preparations for the treatment of urinary-tract disorders. Oval or long buchu, the leaves of *Agathosma crenulata* (*B. crenulata*), has also been used. The name long buchu is also applied to *A. serratifolia* (*B. serratifolia*). The leaves of *A. serratifolia* are also used medicinally.

Buchu leaf oil, usually from *A. betulina*, is occasionally promoted for use in aromatherapy, although it is rarely used in practice.

Homoeopathy

Buchu has been used in homoeopathic medicines under the following names: Barosma; Barosma crenata; Bar. cren.; Barosma serratifolia; Bar. ser.

References.

1. Moolla A, Viljoen AM. Buchu'-*Agathosma betulina* and *Agathosma crenulata* (Rutaceae): a review. *J Ethnopharmacol* 2008; 119: 413–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Althaea Complex†; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; De Witts New Pills†; Extralife Uri-Care†; *Canad.*: Bio Renal†; Cellutex; Diurenat†; Diuretic Tablets; Hepaflor†; Herbal Diretic; Herbal Diuretic†; Herbal Diuretic; Herbal Laxative plus Yogurt†; Saw Palmetto Formula†; Stomach Ease; *Cz.*: Epilobin; *Fr.*: Phytemag; Urophytum†; *S.Afr.*: Borstol Cough Remedy†; Doans Backache Pills†; *Switz.*: Urinex; *UK*: Antitis; Backache Relief; Backache; De Witt's K & B Pills; Diuretabs; HRI Water Balance; Kas-Bah; Lowater; Skin Eruptions Mixture; Watershed; Watershed; *Ukr.*: Uro-Control (Уро-Контрол); *USA*: Cardiopress.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Ger.*: Cysto Hevert.

Bucillamine *(rINN)*

Bucilamina; Bucillaminum; DE-019; SA-96; Tiobutarit; Буциллямин.
N-(2-Mercapto-2-methylpropionyl)-L-cysteine.
$C_7H_{13}NO_3S_2$=223.3
CAS — 65002-17-7.
ATC — M01CC02.
ATC Vet — QM01CC02.
UNII — BB0LRA5WTF.

Pharmacopoeias. In *Jpn.*

Profile

Bucillamine is structurally related to penicillamine (p. 1567.1) and is reported to be an immunomodulator that has been used in the treatment of rheumatoid arthritis.

Adverse effects. Bucillamine has been implicated in the development of skin,[1] kidney,[2,3] and lung disorders.[4]

1. Ogata K, *et al.* Drug-induced pemphigus foliaceus with features of pemphigus vulgaris. *Br J Dermatol* 2001; 144: 421–2.
2. Nagahama K, *et al.* Bucillamine induces membranous glomerulonephritis. *Am J Kidney Dis* 2002; 39: 706–12.
3. Hoshino J, *et al.* Outcome and treatment of bucillamine-induced nephropathy. *Nephron Clin Pract* 2006; 104: c15–c19.
4. Saito Y, *et al.* A case of bucillamine-induced interstitial pneumonia with positive lymphocyte stimulation test for bucillamine using bronchoalveolar lavage lymphocytes. *Intern Med* 2007; 46: 1739–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Rimatil.

Buckwheat

Blé Noir; Boekweit; Boveteort (aerial parts); Buchweizen; Buchweizenkraut (aerial parts); Fagopyri Herba (aerial parts); Grano Turco; Gríkiú zole (aerial parts); Pohanková nať (aerial parts); Sarrasin; Sarrasin Commun; Viljatatar (aerial parts); Ziele gryki; Гречиха Обыкновенная.
ATC Herb — HC05CW5003 (Fagopyrum esculentum: *herb*).
UNII — N0Y68724R3 (Fagopyrum esculentum *grain*); *B10M69172N* (Fagopyrum esculentum).

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

Ph. Eur. 8: (Buckwheat Herb; Fagopyri Herba). The whole or fragmented aerial parts of *Fagopyrum esculentum*, collected in the early flowering period prior to fruiting and dried immediately. It contains a minimum 3.0% of rutoside, calculated with reference to the dried drug.

Profile

The aerial parts of buckwheat, *Fagopyrum esculentum* (Polygonaceae), are included in herbal preparations for chronic venous insufficiency.

Buckwheat contains flavonoids and is a source of rutoside (see p. 2505.3).

Homoeopathy

Buckwheat has been used in homoeopathic medicines under the following names: Fagopyrum; Fagopyrum esculentum; Fago. esc.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Fagorutin Buchweizen†.

Multi-ingredient Preparations. *Fr.*: Tone; *Ger.*: Fagorutin Buchweizen†; *Pol.*: Betasol; Fitoven.

Homoeopathic Preparations. *Austria*: Globuli gegen Sonnenallergie.

Bucladesine Sodium *(rINNM)*

Bucladesina sódica; Bucladésine Sodique; DBcAMP (bucladesine); Dibutyryl Cyclic AMP Sodium; DT-5621 (bucladesine); Natrii Bucladesinum; Натрий Букладезин.
N-(9-β-D-Ribofuranosyl-9*H*-purin-6-yl)butyramide cyclic 3′,5′-(hydrogen phosphate) 2′-butyrate sodium.
$C_{18}H_{24}N_5O_8PNa$=492.4
CAS — 362-74-3 (bucladesine); 16980-89-5 (bucladesine sodium).
ATC — C01CE04.
ATC Vet — QC01CE04.
UNII — 4DZN2C97A7.

Profile

Bucladesine sodium has been reported to have cardiotonic properties when given intravenously. It has been applied topically for the treatment of bedsores.

Bufotenine

Bufotenin; Bufotenina; 5-Hydroxy-*NN*-dimethyltryptamine; Mappine; *NN*-Dimethylserotonin; Буфотенин.
3-(2-Dimethylaminoethyl)indol-5-ol.
$C_{12}H_{16}N_2O$=204.3
CAS — 487-93-4.
UNII — 0A31347TZK.

Profile

Bufotenine is an indole alkaloid obtained from the seeds and leaves of *Piptadenia peregrina*, from which the hallucinogenic snuff cohoba is prepared, and *P. macrocarpa* (Mimosaceae). It was first isolated from the skin glands of toads (*Bufo* spp.) and has also been isolated from species of *Amanita* (Agaricaceae). Bufotenine has serotonergic activity and is reported to have hallucinogenic properties. It has no therapeutic use.

Bugleweed

Profile

The term bugleweed usually refers to species of the genus *Lycopus* (Lamiaceae), although some species of *Ajuga* (Lamiaceae) are also known by this common name.

In herbal medicine, the names bugleweed, sweet bugle, water bugle, and water horehound are applied to both the European bugleweed (*L. europaeus*) and the Virginia bugleweed (*L. virginicus*) which are used mainly for mild hyperthyroidism and menstrual disorders. The American bugleweed (*L. americanus*) is used similarly.

Zelan, the dried aerial part of the hirsute shiny bugleweed (*L. lucidus*) is used in traditional Chinese medicine.

Homoeopathy

Bugleweed has been used in homoeopathic medicines under the following names: Lycopus virginicus; Lycopus virgin.; Lycopus virg.; Lycopus europaeus; Lycopus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: thyreo-loges; Thyreogutt mono.

Homoeopathic Preparations. *Austria*: Asarum Med Complex; *Canad.*: Motherwort Combination 3†; *Fr.*: Badiaga Complexe No 47; Hypophysis Complexe No 31†; Poconeol no 61†; Vespa Complexe No 46†; *Ger.*: Hewethyreon N; Lycoaktin; Neuroselect; Rufebran thyreo†; Thyreo-Injektopas; thyreo-loges comp; Thyreo-Pasc.

Buphenine Hydrochloride *(BANM, rINNM)* ⊗

Bufenina, hidrocloruro de; Buphénine, Chlorhydrate de; Buphenini Hydrochloridum; Hidrocloruro de bufenina; Nylidrin Hydrochloride; Nylidrinium Chloride; Буфенина Гидрохлорид.
1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)propan-1-ol hydrochloride.
$C_{19}H_{25}NO_2HCl$=335.9
CAS — 447-41-6 (buphenine); 849-55-8 (buphenine hydrochloride).
ATC — C04AA02; G02CA02.
ATC Vet — QC04AA02; QG02CA02.
UNII — EC69E3PW7E.

Uses and Administration

Buphenine produces peripheral vasodilatation through beta-adrenoceptor stimulation and a direct action on the arteries and arterioles of the skeletal muscles.

Buphenine has been used in the treatment of peripheral vascular and cerebrovascular disease. Doses of buphenine hydrochloride in the range of 12 to 48 mg daily in 3 or 4 divided doses have been given orally. It has also been used in preparations for rhinitis and nasal congestion.

An intravenous infusion of buphenine hydrochloride has been used to arrest premature labour. It has also been given orally as a prophylactic tocolytic agent.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; buphenine has mainly beta-agonist effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Arlidin; *India*: Arlidin; *Mex.*: Arlidin; Nilken.

Multi-ingredient Preparations. *Austria*: Opino; Opino; *Fr.*: Phlebogel†; *Gr.*: Opino; *Indon.*: Opino†; *Mex.*: Flumil; *Switz.*: Arbid†; Visaline†.

Burnet

Garden Burnet; Greater Burnet; Pimpinela mayor; Salad Burnet; Sanguisorba; Кровохлёбка.
UNII — 4NYV2HT01X (*burnet extract*).

NOTE. Distinguish from Burnet Saxifrage (p. 2463.1).

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

Ph. Eur. 8: (Sanguisorba Root). The whole or fragmented, dried underground parts of *Sanguisorba officinalis* without rootlets. The adventitious roots are about 5 to 25 cm long and up to 2 cm in diameter. They contain a minimum 5.0% of tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1) calculated with reference to the dried drug.

Profile

Burnet, the aerial parts and roots of *Sanguisorba officinalis* (*Poterium officinalis*) (Rosaceae), has antihaemorrhagic and astringent properties. It has been used internally to treat menorrhagia and gastrointestinal disorders and is also used topically for eczema, burns, and other skin disorders.

Burnet is also used as an animal fodder and salad vegetable, and as an ingredient in beer making.

Homoeopathy

Burnet has been used in homoeopathic medicines under the following names: Sanguisorba officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Tormentan; *Indon.*: Ambevent†.

Homoeopathic Preparations. *Fr.*: Cetraria Complexe No 61; Geranium Complexe No 108†.

Burnet Saxifrage

Bibernell; Boucage; Pimpinella; Бедренец Камнеломковый (*Pimpinella saxifraga*).
ATC Herb — HA01WA5003 (Pimpinella major: *root*); *HR05WA5034* (Pimpinella major: *herb*); *HR05WA5037* (Pimpinella saxifraga: *root*); *HJ01WB5011* (Pimpinella saxifraga: *root*); *HA03AW5050* (Pimpinella saxifraga: *root*); *HA01WA5004* (Pimpinella saxifraga: *root*); *HR05WA5036* (Pimpinella saxifraga: *herb*); *HC05BW5003* (Pimpinella major: *herb*); *HC05BW5004* (Pimpinella saxifraga: *herb*); *HA09WX5001* (Pimpinella major: *herb*); *HA09WX5002* (Pimpinella saxifraga: *herb*); *HR05WA5035* (Pimpinella major: *root*); *HJ01WB5010* (Pimpinella major: *root*); *HA03AW5049* (Pimpinella major: *root*).
UNII — 8O53J9196C (Pimpinella); *5Y05905N7G* (Pimpinella saxifraga).

NOTE. Distinguish from Burnet (p. 2462.3).

Profile

The root of burnet saxifrage, *Pimpinella saxifraga* (Apiaceae), or greater burnet saxifrage, *P. major* is included in herbal preparations for coughs and minor upper respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel; *Canad.*: Honey Herb Cough Drops†; Original Herb Cough Drops†; *Ger.*: Cefabronchin; *Neth.*: Bronchicum; *Pol.*: Bronchicum Eliksir†; *Switz.*: Kernosan Elixir; Kernosan Heidelberger Poudre; Makaphyt Gouttes antitussives†.

Butcher's Broom

Box Holly; Dygiųjų pelžiedžių šakniastiebiai; Kłącze ruszczyka; Listnatcový kořen; Mäusedornwurzelstock; Petit houx; Rautamyrtinjuurakko; Rusci Radix; Rusci rhizoma; Stickmyrtenrot; Иглица Шиповатая (*Ruscus aculeatus*).
ATC Herb — HC05AW5006 (Ruscus aculeatus: *rhizome*); *HC05BW5005* (Ruscus aculeatus: *rhizome*).
UNII — 5KEZ82GMGU (Ruscus aculeatus); *ZW12V95I1Q* (Ruscus aculeatus *root*).

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

Ph. Eur. 8: (Butcher's Broom; Rusci Rhizoma). The dried, whole or fragmented underground parts of *Ruscus aculeatus*. It contains a minimum of 1.0% of total sapogenins, expressed as ruscogenins (mixture of neoruscogenin ($C_{27}H_{40}O_4$ = 428.6) and ruscogenin), calculated with reference to the dried drug. Protect from light.

Profile

The dried rhizome and root of butcher's broom is used in herbal preparations for chronic venous insufficiency and haemorrhoids. It contains steroidal saponins including the sapogenin ruscogenin (see p. 2608.3) which is used for similar purposes. The dose may be expressed in terms of total ruscogenins.

References.
1. Anonymous. *Ruscus aculeatus* (butcher's broom). *Altern Med Rev* 2001; 6: 608–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Venoserin; *Ger.*: Cefadyn; Fagorutin Ruscus†; Phlebodril Venenkapseln; *Spain*: Arkocapsulas Rusco; *Switz.*: Impuls pour les veines; *UK*: Phytovein; *Ukr.*: Cyclo 3 Fort (Цикло 3 Форт).

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; Celu-Atlas; Cistidac; CVP Cellulite; CVP Flebo; Cyclo 3; Fiblast; Nolen; Varicofem; Varicura; Venart Crema; Venart; Venidium; *Austral.*: Aesculus & Ruscus Compound; Extralife Leg-Care†; Horsechestnut Complex; *Braz.*: Capilos; *Chile*: Anastim; Celu-Atlas; *Cz.*: Cyclo 3 Fort; *Fr.*: Anaphase; Avene Antirougeurs; Bicirkan; Climaxol; Creme au Melilot Composee†; Cyclo 3 Fort; Cydo 3; Diveine; Evarose†; Rap Phyto; Veinobiase; *Ger.*: Phlebodril†; *Gr.*: Cyclo 3 Forte; *Indon.*: Haemogal; Venos; *Ital.*: Angiorex Complex; Capill Venogel; Clebolider†; Fleboliden; Slimmer Plus; Wasotonal†; *Mex.*: Fabroven; *Pol.*: Cyclo 3 Fort; *Port.*: Creme Laser Hidrante†; Cyclo 3; *Rus.*: Cyclo 3 (Цикло 3); Cyclo 3 Fort (Цикло-3 Форт); *Singapore*: Cyclo 3 Fort; Cyclo 3†; Pedimed Foot Care Cream; *Spain*: Fabroven†; Fabroven; *Switz.*: Phlebodril N; Phlebodril; Silence†; *Thai.*: Cyclo 3 Fort; *Venez.*: Anastim.

Butinoline Phosphate *(rINN)*

Butinolina, fosfato de; Butinoline, Phosphate de; Butinolini Phosphas; Fosfato de butinolina; Бутинолина Фосфат.
1,1-Diphenyl-4-pyrrolidino-1′-yl but-2-yn-1-ol phosphate.
$C_{20}H_{21}NO,H_3PO_4$=389.4.
CAS — 968-63-8 (butinoline); 54118-66-0 (butinoline phosphate).
UNII — EB2657YYBG.

Profile

Butinoline phosphate is used as an antispasmodic in preparations for gastrointestinal disorders.

Butterbur

Белокопытник.
ATC Herb — HN02CW5003 (Petasites hybridus: *leaf*); *HR03WX5007* (Petasites hybridus: *leaf*); *HA03WX5005* (Petasites hybridus: *rhizome*); *HG02WB5005* (Petasites hybridus: *leaf*); *HG04BX5001* (Petasites hybridus: *rhizome*); *HA03WX5004* (Petasites hybridus: *leaf*); *HN02CW5004* (Petasites hybridus: *rhizome*); *HR03WX5008* (Petasites hybridus: *rhizome*).

Profile

The leaves and roots of butterbur, *Petasites hybridus* (*P. officinalis*) (Asteraceae), have antispasmodic and anti-inflammatory properties and have been used in herbal preparations for a variety of disorders, including gastrointestinal and respiratory-tract disorders, and migraine. However, the MHRA in the UK advises against its use because of reports of hepatotoxicity (see Effects on the Liver, below).

References.
1. Schapowal A. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *BMJ* 2002; 324: 144–6.
2. Lee DK, *et al.* Butterbur, a herbal remedy, attenuates adenosine monophosphate induced nasal responsiveness in seasonal allergic rhinitis. *Clin Exp Allergy* 2003; 33: 882–6.
3. Diener HC, *et al.* The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol* 2004; 51: 89–97.
4. Jackson CM, *et al.* The effects of butterbur on the histamine and allergen cutaneous response. *Ann Allergy Asthma Immunol* 2004; 92: 250–4.
5. Lipton RB, *et al.* Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004; 63: 2240–4.
6. Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache* 2005; 45: 196–203.
7. Giles M, *et al.* Butterbur: an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; 5: 119–43.
8. Käufeler R, *et al.* Efficacy and safety of butterbur herbal extract Ze 339 in seasonal allergic rhinitis: postmarketing surveillance study. *Adv Therapy* 2006; 23: 373–84.
9. Agosti R, *et al.* Effectiveness of Petasites hybridus preparations in the prophylaxis of migraine: a systematic review. *Phytomedicine* 2006; 13: 743–6.
10. Sadler C, *et al.* American Academy of Pediatrics Provisional Section on Complementary, Holistic, and Integrative Medicine. Complementary, holistic, and integrative medicine: butterbur. *Pediatr Rev* 2007; 28: 235–8. Correction [dose error]. *ibid.*: 385.
11. Sutherland A, Sweet BV. Butterbur: an alternative therapy for migraine prevention. *Am J Health-Syst Pharm* 2010; 67: 705–11.

Effects on the liver. Butterbur contains pyrrolizidine alkaloids and sesquiterpenes which have been implicated in serious liver damage and organ failure; 40 cases of hepatotoxicity associated with butterbur preparations have been reported in the literature including 9 cases of acute hepatitis, 2 of which required transplantation. Consequently, the MHRA in the UK has advised against their use.[1]

1. MHRA. Press release: unlicensed herbal remedy could cause liver and organ damage (issued 1st February, 2012). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON143514 (accessed 23/02/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Petadolex†; *Switz.*: Pollivita; Tesalin Allergy†; Tesalin N.

Multi-ingredient Preparations. *Switz.*: Dragees aux figues avec du sene; Dragees pour la detente nerveuse†; Relaxane; Valverde Constipation dragees; Valverde Detente dragees; Wala Baume pectoral au plantain; Wala Pulmonium suc contre la toux.

Homoeopathic Preparations. *Fr.*: Kalium Muriaticum Complexe No 41†; Santalum Complexe No 30†; *Switz.*: metaneuron N.

Butternut

Buttermussbaum (Buttermussbaum); Juglans; Lemon Walnut; Nogal Ceniciento; Noyer Cendré; Oil Nut; White Walnut.

NOTE. Distinguish from English Walnut (p. 2646.1) and Black Walnut (p. 2646.1). The name Juglans has also been applied to English Walnut.

Profile

The inner bark or inner root bark of the butternut, *Juglans cinerea* (*J. cathartica*; *J. oblonga*; *Wallia cinerea*), Juglandaceae, is reported to have stimulant laxative properties. It is included in herbal preparations for gastrointestinal and biliary disorders. It has also been used for skin disorders.

Homoeopathy

Butternut has been used in homoeopathic medicines under the following names: Juglans cinerea; Juglans cin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Colax†; GR² Control Thermogenic Enhancer; *Canad.*: Para-Gard; *UK*: Adios; Boldex.

Homoeopathic Preparations. *Fr.*: Agnus Castus Complexe No 2†; Cistus Canadensis Complexe No 86†; *Ger.*: Cholo 2-injektopas; Relivora Komplex.

Butyl Nitrite

n-Butyl Nitrite; Nitrito de butilo; Nitrous Acid Butyl Ester; Бутилнитрит.
$C_4H_9NO_2$=103.1.
CAS — 544-16-1.
UNII — 44P8QG0F3T.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of butyl nitrite:

Bolt; Climax; Locker room; Poppers; Rush; Snappers; Video head cleaner.

Profile

Butyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p. 1540.3).

Cadmium

Cadmio; Kadm; Kadmium; Кадмий.
Cd=112.411.
CAS — 7440-43-9.
UNII — 00BH33GNGH.

Cadmium Sulfate

Cadmii Sulfas; Cadmium, sulfate de; Kadmiumsulfaatti; Kadmiumsulfat; Kadmu siarczan.
$CdSO_4$=208.5
CAS — 10124-36-4.
UNII — 947UNF3Z6O.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Cadmium Sulfate Hydrate for Homoeopathic Preparations; Cadmii Sulfas Hydricus ad Praeparationes Homoeopathicas). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol.

Profile

Cadmium is used in many manufacturing processes and cadmium poisoning presents a recognised industrial hazard. Inhalation of cadmium fumes during welding procedures may not produce symptoms until 12 to 36 hours have passed and these symptoms include respiratory distress leading to pulmonary oedema. Ingestion of cadmium or its salts has the additional hazard of severe gastrointestinal effects. Cadmium has a long biological half-life and accumulates in body tissues, particularly the liver and kidneys. Chelation therapy is not generally recommended for cadmium poisoning, although sodium calcium edetate has been used after acute ingestion. However, chelators do not increase cadmium elimination in chronic poisoning and use of dimercaprol may increase cadmium toxicity and should be avoided. Chronic exposure to cadmium results in progressive renal impairment and other effects (see p. 2464.1).

Cadmium sulfide has been used topically in some countries for the treatment of skin and scalp conditions. Cadmium sulfate has been included in some preparations for the treatment of eye irritation.

Homoeopathy

Cadmium and some cadmium compounds have been used in homoeopathic medicines under the following names:

- Cadmium metallicum; Cadmium met; Cad. met.
- Cadmium chloride: Cadmium muriaticum; Cadmium mur

- Cadmium iodide: Cadmium iodatum; Cadmium iod
- Cadmium sulfate: Cadmium sulfuricum; Cadmium sulphuricum; Cad. sul.
- Cadmium sulphide: Cadmium sulphuratum; Cad. sulph.

For other cadmium compounds used in homoeopathic medicines see Cadmium Bromide, under Sodium Bromide, p. 2461.1.

Adverse effects. The toxicity of cadmium has been reviewed.[1] Environmental or occupational exposure to cadmium has been associated with renal dysfunction,[2-5] although this may be reversible if exposure is reduced.[4] A reduction in bone density may also occur.[7] Fatalities due to industrial exposure or self-poisoning have also been reported.[8,9] No effect on testicular endocrine function was noted in 77 industrial workers exposed to cadmium.[3]

An increased incidence of cancer of the prostate has been reported in subjects exposed to high levels of cadmium but the evidence is not conclusive.[10] There may be an association between cadmium exposure and lung cancer, although observations on this type of cancer are difficult to interpret because of exposure to other hazards such as smoking.

1. Fielder RJ, Dale EA. Cadmium and its compounds. *Toxicity Review 7*. London: HMSO, 1983.
2. Buchet JP, *et al.* Renal effects of cadmium body burden of the general population. *Lancet* 1990; 336: 699–702. Correction. *ibid.* 1991; 337: 1554.
3. Mason HJ. Occupational cadmium exposure and testicular endocrine function. *Hum Exp Toxicol* 1990; 9: 91–4.
4. Cai S, *et al.* Renal dysfunction from cadmium contamination of irrigation water: dose-response analysis in a Chinese population. *Bull WHO* 1998; 76: 153–9.
5. Satarug S, *et al.* Safe levels of cadmium intake to prevent renal toxicity in human subjects. *Br J Nutr* 2000; 84: 791–802.
6. Hotz P, *et al.* Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. *Lancet* 1999; 354: 1508–13.
7. Staessen JA, *et al.* Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. *Lancet* 1999; 353: 1140–44.
8. Taylor A, *et al.* Poisoning with cadmium fumes after smelting lead. *BMJ* 1984; 288: 1270–1.
9. Buckler HM, *et al.* Self poisoning with oral cadmium chloride. *BMJ* 1986; 292: 1559–60. Correction. *ibid.*; 293: 236.
10. Bell GM. Carcinogenicity of cadmium and its compounds. *Toxicity Review 24*. London: HMSO, 1991.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Biocadmio†.

Homoeopathic Preparations. *Fr.*: Conium Complexe No 36†; *Ger.*: Rufebran gastro†.

Cajuput Oil

Cajeput Oil; Cajuput Essence; Cayeput, aceite esencial de; Esencia de cayeput; Oleum Cajuputi; Каепутовое Масло.
UNII — J3TO68UO37.

NOTE. Do not confuse with Cineole (p. 2479.1), which has the similar synonyms, cajupetol and cayeputol.

Profile

Cajuput oil is a volatile oil obtained by distillation from the fresh leaves and twigs of *Melaleuca cajuputi* (*M. leucadendron*) (Myrtaceae). It contains cineole (p. 2479.1). Cajuput oil has been applied externally as a stimulant and mild rubefacient in rheumatism. It is also used with other volatile agents in preparations for the relief of respiratory-tract disorders and nasal congestion. It is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Goanna Heat Cream; Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; *Austria*: Babix; Tiger Balsam Rot; Tiger Balsam Weiss; *Belg.*: Olbas; *Canad.*: External Anti-Pain Oil†; Penetrating Rub†; Tiger Balm Arthritis Rub; Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; Youngflex Massage 168; *Fr.*: Tigre de Chine; *Ger.*: Liniplant; Olbas; Tiger Balm rot N; Tiger Balm weiss; *Gr.*: Tiger Balm; *Hong Kong*: BF-Analgesic Balm†; Vida Salirub†; *Hung.*: Tiger Balm Red; Tiger Balm White; *India*: Flexi-muv†; *Indon.*: Balsam Sakti†; Minyak Telon Cap Tiga Anak†; Minyak Telon†; Telon 3 Anak; *Irl.*: Olbas; Olbas; Tiger Balm Red; Tiger Balm White; *Israel*: Tiger Balm Red; Tiger Balm White; *Neth.*: Olbas†; *Philipp.*: Begesic; *Pol.*: Argol Rheuma; Olbas; Olbas; *S. Afr.*: Muscle Rub†; *Swed.*: Oleum Basileum; Oleum Salvum; *Switz.*: Baume du Tigre blanc; Baume du Tigre rouge; Novital; Olbas†; Olbas; Olbas; Wala Baume nasal; *Thai.*: Dexalin Balm; Hot Ize; *UK*: Bells Muscle Rub; Olbas for Children; Olbas; Olbas; Soothol; Tiger Balm; Vadarex; *USA*: Tiger Balm.

Calamus

Acore Vrai; Ácoro aromático; Ácoro verdadero; Calamo aromático; Calamus Rhizome; Kalmus; Sweet Flag Root; Аир Обыкновенный (*Acorus calamus*).
CAS — 8015-79-0 (calamus oil).
ATC Herb — HA03AW5002 (Acorus calamus: rhizome).
UNII — XY1K7KIQ0F (Acorus calamus).

Pharmacopoeias. In *Chin.* and *Swiss*.

Profile

Calamus, the dried rhizome of the sweet flag, *Acorus calamus* (Acoraceae), has been used as a bitter and carminative; it is also used as a source of calamus oil, which is employed in perfumery. The FDA in the USA has prohibited marketing calamus as a food or food additive; the oil (Jammu variety) is reported to be a carcinogen.

Homoeopathy

Calamus has been used in homoeopathic medicines under the following names: Calamus aromaticus; Acorus calamus.

References.

1. Björnstad K, *et al.* Bioanalytical investigation of asarone in connection with Acorus calamus oil intoxications. *J Anal Toxicol* 2009; 33: 604–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Koren Puskvorce†.

Multi-ingredient Preparations. *Austria*: Abdomilon N; Pervivo; *Canad.*: Gallexier†; *Cz.*: Dr Theiss Schwedenbitter†; Original Schwedenbitter; Stomaran; *Fr.*: Jouvence de l'Abbe Soury; NurAiD; *Ger.*: Abdomilon N; ventri-loges N†; *Hung.*: Bano Svedkeseru; Bittner; *Israel*: Rekiv†; *Pol.*: Dentosept A; Gastro†; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; Seboren; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Phytogastrol (Фитогастрол); Stomatophit (Стоматофит); Vicair (Викаир); Vicalin (Викалин); *Singapore*: NeuroAid; *Switz.*: Kernosan 26; Kernosan Elixir; Tisane pour l'estomac; Urinex; Wala Elixir amer; *UK*: Pegina; *Ukr.*: Pilex (Пилекс); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†; Vicair (Викаир); Vicalin (Викалин); Vitokan (Витокан).

Homoeopathic Preparations. *Fr.*: Carominthe; *Ger.*: Infi-Symphytum; Steirocall.

Calcium Carbimide *(rINN)*

Calcii Carbimidum; Calcium Cyanamide; Carbimida cálcica; Carbimide Calcique; Cyanamide; Кальция Карбимид.
$CCaN_2$=80.1
CAS — 156-62-7 (calcium carbimide); 8013-88-5 (citrated calcium carbimide).
ATC — N07BB02.
ATC Vet — QN07BB02; QV03AA02.
UNII — ZLR270912W.

NOTE. The name cyanamide is also used to designate carbimide, which is used in veterinary medicine.

Profile

Calcium carbimide has actions and uses similar to those of disulfiram (p. 2495.3). It is an aversive agent used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p. 1734.1) and causes a reaction in patients who have consumed alcohol similar to that seen with disulfiram (see p. 2496.1). It is given orally in a dose of up to 60 mg twice daily. Citrated calcium carbimide has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Colme†; *Rus.*: Colme (Колме); *Spain*: Colme.

Calcium Dihydrogen Phosphate

Acid Calcium Phosphate; Calcium Dihydrogenphosphoricum; E341; Fosfato monocálcico; Monobasic Calcium Phosphate; Monobasic Calcium Phosphate, Monohydrate; Monocalcium Phosphate; Кальция Дигидрофосфат.
Calcium tetrahydrogen diorthophosphate monohydrate.
$Ca(H_2PO_4)_2.H_2O$=252.1
CAS — 7758-23-8 (anhydrous calcium dihydrogen phosphate).
UNII — 701EKV9RMN (anhydrous calcium dihydrogen phosphate); 0N4E6L5449 (calcium dihydrogen phosphate monohydrate).

Pharmacopoeias. In *Jpn* and *Swiss*.

Profile

Calcium dihydrogen phosphate is used in fertilisers. It is also used as an antoxidant in baking powders and flours and as a source of calcium in some mineral supplement preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Phosphoneuros; *India*: Caracsol; *Ukr.*: Pregnavit (Пренавит).

Calcium Dobesilate *(rINN)*

205E; Calcii Dobesilas; Calcium dobésilate de; Calciur Doxybenzylate; CLS-2210; Dobesilan vápenatý; Dobésilat de Calcium; Dobesilato de calcio; Kalcio dobesilatas; Kalciumdobesilat; Kalcium-dobezilát; Kalsiumdobesilaatt; Kalsiyum Dobesilat; Кальция Добезилат.
Calcium 2,5-dihydroxybenzenesulphonate.
$C_{12}H_{10}CaO_{10}S_2$=418.5
CAS — 88-46-0 (dobesilic acid); 20123-80-2 (calcium dobesilate).
ATC — C05BX01.
ATC Vet — QC05BX01.
UNII — 5921X1560Q (anhydrous calcium dobesilate); M0ROX9374L (calcium dobesilate monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii) which specifies th monohydrate.

Ph. Eur. 8: (Calcium Dobesilate Monohydrate). A white o almost white hygroscopic powder. Very soluble in water freely soluble in dehydrated alcohol; practically insoluble i dichloromethane; very slightly soluble in isopropyl alcohol A 10% solution in water has a pH of 4.5 to 6.0. Store i airtight containers. Protect from light.

Profile

Calcium dobesilate is claimed to reduce capillary permeability and has been used in various peripheral circulatory disorders including diabetic retinopathy and haemorrhoids (p. 1808.1). Gastrointestinal disturbances have occurred with its use, and there are also reports of hypersensitivity reactions.

Calcium dobesilate is given orally in usual doses of 0.5 to 1.5 g daily in divided doses. It is also given rectally for haemorrhoids and is an ingredient of some preparations given for various skin disorders.

Adverse effects. Agranulocytosis has been reported[1-3] in a few patients after treatment with calcium dobesilate, and in 2 cases recurred on rechallenge.[1,2] However, a later review[4] of the safety profile of calcium dobesilate concluded that the overall risk of adverse effects was low with the most prominent symptoms being fever, arthralgias, and gastrointestinal disturbances. Reports of agranulocytosis were rare and the authors concluded that there may have been methodological bias in previous assessments of risk.

1. Kulessa W, *et al.* Wiederholte Agranulozytose nach Einnahme von Calciumdobesilat. *Dtsch Med Wochenschr* 1992; 117: 372–4.
2. Cladera Serra A, *et al.* Agranulocitosis inducida por dobesilato cálcico. *Med Clin (Barc)* 1995; 105: 558–9.
3. García Benayas E, *et al.* Calcium dobesilate-induced agranulocytosis. *Pharm World Sci* 1997; 19: 251–2.
4. Allain H, *et al.* Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Safety* 2004; 27: 649–60.

Uses. Although there have been reports from small studies of a positive effect of calcium dobesilate in patients with diabetic retinopathy, the conclusion from a large multicentre, randomised, double-blind, placebo-controlled study was that it neither prevented the occurrence of nor reduced the probability of developing clinically significant macular oedema during the 5-year follow-up period in patients with type 2 diabetes mellitus and mild-to-moderate non-proliferative diabetic retinopathy.[1]

1. Haritoglou C, *et al.* Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2009; 373: 1364–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Doxium; Duflemina; Eflevar; *Austria*: Doxium; *Chile*: Doxium; *China*: An Duo Ming (安多明); Dashiming (达士明); Doxium (导升明)†; Hao Chang (昊畅); Keyuan (可元); Li Bei Si (利倍思); Medoril (美多瑞); *Cz.*: Danium; Dobica; Doxium; *Ger.*: Dexium†; Dobica†; *Gr.*: Difilina; Doxytrex; Nugatex; Stifarol; *Hong Kong*: Doxium; *Hung.*: Doxilek; Doxium; *India*: Cabisyl; Caldob; Cocalate; DBS; Dobesil; Dobest; Dobilet; Dobkair; Dosil; Doxium; Eflo; Mobium; *Ital.*: Doxium; *Malaysia*: Doxium; *Mex.*: Doxium; *Mon.*: Doxium; *Philipp.*: Doxium; *Pol.*: Doxium; Galvenox; *Port.*: Doxi-Om; Doxivenil; *Rus.*: Doxi-Hem (Доксн-хем); *S.Afr.*: Doxium†;

Spain: Doxium; ***Switz.:*** Doxium; ***Turk.:*** Doxium; Modet; ***Venez.:*** Deoxical; Doxium.

Multi-ingredient Preparations. ***Cz.:*** Dobexil; Doxiproct Plus; Doxiproct; ***Hung.:*** Doxiproct Plus; Doxiproct; Doxivenil†; ***Ital.:*** Doxiproct; ***Mex.:*** Doxiproct Plus; Vasculflow; ***Port.:*** Doxiproct Plus; Doxiproct; ***Switz.:*** Doxiproct Plus; Doxiproct; Doxivenil†; ***Venez.:*** Doxivenil.

Calcium Hopantenate *(rINNM)*

Calcii Hopantenas; Calcium Homopantothenate; Hopanténate de Calcium; Hopantenato cálcico; Кальций Гопантенат.
Calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethylbutyramido) butyrate hemihydrate.
$Ca(C_{10}H_{18}NO_5)_2,\frac{1}{2}H_2O$=513.6
CAS — 18679-90-8 (hopantenic acid); 17097-76-6 (anhydrous calcium hopantenate); 1990-07-4 (calcium hopantenate hemihydrate).
UNII — LK8EOC1M6K (anhydrous calcium hopantenate); RQA63PEI5Q (calcium hopantenate hemihydrate).

Profile

Calcium hopantenate is a homologue of pantothenic acid (p. 2085.2) and has been given orally in the treatment of various behavioural, extrapyramidal, and other neurological disorders. Its use is limited by severe metabolic adverse effects and fatalities have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.:*** Gopantam (Гопантам); Pantocalcin (Пантокальцин); Pantogam (Пантогам); ***Ukr.:*** Pantocalcin (Пантокальцин); Pantogam (Пантогам)†.

Calcium Hydroxide

Cal apagada; Cal hidratada; Calcii Hydroxidum; Calcium Hydrate; Calcium, hydroxyde de; Calciumhydroxid; E526; Hidróxido cálcico; Hydroxid vápenatý; Kalcio hidroksidas; Kalcium-hidroxid; Kalciumhydroxid; Kalsiumhydroksidi; Slaked Lime; Wapnia wodorotlenek; Гидроокись Кальция; Гашёная Известь.
$Ca(OH)_2$=74.09
CAS — 1305-62-0.
UNII — PF5DZW74VN.

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

Ph. Eur. 8: (Calcium Hydroxide). A fine white or almost white powder. Practically insoluble in water.

USP 36: (Calcium Hydroxide). A white powder with a slightly bitter alkaline taste. Soluble 1 in 630 of water and 1 in 1300 of boiling water; insoluble in alcohol; soluble in glycerol and in syrup. Store in airtight containers.

Profile

Calcium hydroxide is a weak alkali. It is used in the form of Calcium Hydroxide Solution (lime water) in some skin lotions and oily preparations to form calcium soaps of fatty acids which produce water-in-oil emulsions.

Calcium hydroxide pastes are used in dentistry. A paste made from a mixture of calcium hydroxide and potassium hydroxide and known as Vienna paste was used as an escharotic. Soda lime (p. 2617.2) is a mixture of calcium hydroxide and potassium hydroxide and/or sodium hydroxide. With sulfur, calcium hydroxide forms sulfurated lime solution (p. 1721.3).

Homoeopathy

Calcium hydroxide has been used in homoeopathic medicines under the following names: Calcarea caustica; Cal. caus.; Calc caust.

Adverse effects. A report of ocular alkali burns in children, leading to severe visual loss, caused by packets of calcium hydroxide ('Chuna') popularly consumed in India as an additive to chewing tobacco.[1]

For the use of sodium edetate in the treatment of calcium hydroxide burns of the eye, see p. 1551.1.

1. Agarwal T, Vajpayee RB. A warning about the dangers of chuna packets. *Lancet* 2003; **361:** 2247.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.:*** Calcipulpe†; ***Ger.:*** Dermi-cyl†; ***Mex.:*** Oleoderm.

Multi-ingredient Preparations. ***Gr.:*** Calvicef; ***Mex.:*** Liniderm; Oleoderm Plus; ***Pol.:*** Acne Sulf†; ***Spain:*** Cremsol†.

Pharmacopoeial Preparations
BP 2014: Calcium Hydroxide Solution;
USP 36: Calcium Hydroxide Topical Solution.

Calcium Oxide

Cal viva; Calcii Oxidum; Calcium Oxydatum; Calcium, oxyde de; Calx; Calx Usta; Chaux Vive; E529; Gebrannter Kalk; Lime; Óxid cálcico; Oxid vápenatý; Óxido de calcio; Quicklime; Wapnia tlenek; Окись Кальция.
CaO=56.08
CAS — 1305-78-8.
ATC Vet — QP53AX18.
UNII — C7X2M0VVNH.

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

USP 36: (Lime). Hard, odourless, white or greyish-white masses, granules, or powder. When it is moistened with water a reaction occurs, heat being evolved and calcium hydroxide formed. Slightly soluble in water; very slightly soluble in boiling water. Store in airtight containers.

Uses and Administration

Calcium oxide has been used in various dermatological preparations. A paste made from a mixture of calcium oxide and sodium hydroxide and known as London paste was used as an escharotic.

Adverse Effects and Treatment

Calcium oxide may cause burns on contact with moist skin and mucous membranes; it is particularly irritant to the eyes. Washing or flooding of affected areas may need to be prolonged. Pneumonitis may follow inhalation.

For the use of sodium edetate in the treatment of calcium oxide burns of the eye, see p. 1551.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.:*** Oleo Calcarea.

Dried Calcium Sulfate

Calcii Sulfas Hemihydricus; Calcined Gypsum; Calcium Sulfuricum ad Usum Chirurgicum; Calcium Sulphuricum Ustum; Dried Calcium Sulphate; Exsiccated Calcium Sulphate; Gebrannter Gips; Gesso; Gypsum Siccatum; Plaster of Paris; Plâtre Cuit; Síran vápenatý hemihydrát; Sulfato cálcico anhidro; Sulfato de calcio anhidro; Sulphate of Lime; Yeso Blanco; Yeso de Paris; Сульфат Кальция (calcium sulfate); Сернокислый Кальций (calcium sulfate).
$CaSO_4,\frac{1}{2}H_2O$=145.1
CAS — 10034-76-1 (calcium sulfate hemihydrate); 26499-65-0 (calcium sulfate hemihydrate).
UNII — 3RW091J48V.

Pharmacopoeias. In *Br., Chin., Ger., Jpn, Pol.,* and *Viet.*

BP 2014: (Dried Calcium Sulfate). A white or almost white, odourless or almost odourless hygroscopic powder. It may contain suitable setting accelerators or decelerators. Slightly soluble in water; more soluble in dilute mineral acids; practically insoluble in alcohol.

The BP gives Exsiccated Calcium Sulphate and Plaster of Paris as approved synonyms.

Profile

Dried calcium sulfate is used for the preparation of Plaster of Paris Bandage, which is used for the immobilisation of limbs and fractures. It is also employed for making dental casts and has been used as a bone graft substitute.

Calendula

Caléndula; Calendulae Anthodium; Calendulae Flos; Flor de muerto; Gold-bloom; Kehäkukka; Körömvirág; Koszyczek nagietka; Maravilla; Marigold; Marybud; Medetkų žiedai; Mercadela; Měsíčkový květ; Pot Marigold; Ringblomma; Souci; Ноготки.
ATC Herb — HD02WX5002 (Calendula officinalis: flower); HD03WX5004 (Calendula officinalis: flower); HC05AW5002 (Calendula officinalis: flower); HD03WX5005 (Calendula officinalis: herb).
UNII — 18E7415PXQ (calendula); P0M7O4Y7YD (Calendula officinalis flower).

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

Ph. Eur. 8: (Calendula Flower). It consists of the whole or cut, dried, and fully opened flowers which have been detached from the receptacle of the cultivated, double-flowered varieties of *Calendula officinalis*. It contains not less than 0.4% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12}$=464.4) calculated with reference to the dried drug. Protect from light.

Profile

Calendula has antiseptic, anti-inflammatory, and astringent properties. It is used in external preparations for minor skin disorders, and also internally for gastrointestinal and menstrual disorders. Calendula is also included in many herbal preparations to improve their appearance.

Calendula oil is also used.

Homoeopathy

Calendula has been used in homoeopathic medicines under the following names: Calendula officinalis; Calend.

References.

1. Anonymous. Final report on the safety assessment of Calendula officinalis extract and Calendula officinalis. *Int J Toxicol* 2001; **20** (suppl 2): 13–20.
2. WHO. Flos Calendulae. *WHO Monographs on Selected Medicinal Plants,* volume 2. Geneva: WHO; 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/6.html (accessed 04/02/10)
3. Basch E, *et al.* Natural Standard Research Collaboration. Marigold (*Calendula officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2006; **6:** 135–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.:*** Spin-Care; ***Cz.:*** Dr Theiss Ringelblumen Salbe†; Mesickovy†; ***Fr.:*** Calendulene†; ***Hung.:*** Plerico; ***Irl.:*** Calendolon; ***Mex.:*** Cicadin; ***Pol.:*** Calendulin†; ***UK:*** Calendolon.

Multi-ingredient Preparations. ***Arg.:*** Acnetrol; Albion; Aristaloe; Brunavera; Bushi; Capson; Control Acne; Eurocolor Post Solar; Lactoscrub; Lavandula Oligoplex; Talquisedan; ***Austral.:*** Aloe Vera Gel; Arctium & Zinc Compound; Bio-Oil; Eczema Relief†; Herbal Throat Spray; Nappy Rash Relief Cream; Skin Support; ***Austria:*** Nasenol; The Chambard-Tee; ***Braz.:*** Cetrilan; Malvatricin Natural†; ***Canad.:*** Formula T13 Tea†; Formula T4†; Pure Gardens; ***Chile:*** Matikomp; Talquisedan; ***Cz.:*** Cicaderma; Epilobin; ***Fr.:*** Blue Berry; Cicatridine; Dida; Glycepure; Homeoplasmine; Olioseptil Gorge-Larynx; Santane F_{10}†; Saugella allaitment anti-crevasses; Saugella douceur Poligyn; Saugella Girl; Saugella HydraSerum; Stimunal; ***Ger.:*** Euphrasia comp; Unguentum lymphaticum†; Weleda Nasenol; ***Hong Kong:*** Calmiderm; Pregnacare; ***Hung.:*** Aranyer Elleni; Depsorin; Gastrosol; Plerudin; Rheuvit; Szent Lukacs; Venen; ***India:*** Dermec; ***Ital.:*** Alkagin; Allerlux; Babygella; Decon Ovuli; Emoform Alifresh; Faringel; Fito Stomygen†; Lenirose; Nevril; Proctopure; Sclerovis H Plus; Vaginol; Zeadema Crono; ***Malaysia:*** A-Bruzzy; Arnica Comp; Bio-Oil; Natberry Extra; ***Mex.:*** Aloemagnolia; Sanicut; Suavene; Supranettes Naturalag; ***Neth.:*** Bioforce; ***Philipp.:*** Lactaderm†; ***Pol.:*** Arcalen; Azucalen; Dyspepsin; Escalar; Mucosit; Padma 28; Reumosol; Sanofil; Scaldex; ***Port.:*** Alkagin; Alkagin; Alkagin; Cicaderma; ***Rus.:*** Alorom (Алором); Elecasol (Элекасол); GeKaTon (Жекатон); Kliophyt (Клиофит); Pectorales Species No 4 (Грудной Сбор 4); Phytonefrol (Фитонефрол); Rotocan (Ротокан); ***S.Afr.:*** Heilsalbe†; Oleum Rhinale Nasal Oil†; Wecesin†; ***Singapore:*** A-Bruzzy; Nu-Derm Toner; ***Spain:*** Banoftal†; ***Switz.:*** Arteria-vita; Echinadoron; Gel de consoude†; Impuls a la consoude; Keppur; Onguent aux herbes Keller; Urinex; Venaphyt N; Wala Echinacea; Wecesin; Ziegella†; ***Turk.:*** Alkagin; ***UK:*** Calendula Nappy Change Cream; Eucanol; Massage Balm with Calendula; Padma Circosan; Supranettes; ***Ukr.:*** Clotrex (Клотрекс); Elecasol (Элекасол); Pilex (Пилекс); Tazalok (Тазалок); Venen Theiss (Венен Тайсс); Vitokan (Витокан); ***USA:*** Miaderm Radiation Relief; Nasal-Ease; ***Venez.:*** Andantol Jalea; Flucirac; Gelsem; Linfoderm.

Homoeopathic Preparations. ***Austral.:*** Echine†; Homoderma; Sedatif†; ***Austria:*** Calendumed; Lymphdiaral; Lymphdiaral; Repisan; Sonnenbrandspray; Traumeel; Tropfen bei Verletzungen; ***Canad.:*** Arnica Cream†; Calendula +; Calendula Ointment†; Capsicum + Arthri-Cream; Cicaderma†; ClearAc Cleanser†; Erinol†; Formula MBC†; Homeoplasmine; Homeovox; Optalia†; Sedatil; Traumeel; ***Chile:*** Calendaderm; Calendula Echinacea Comp; Matico Compuesto; Ovukalen; ***Cz.:*** Homeovox; Sedatif PC; Traumeel; ***Fr.:*** Calendula Complexe No 89; Cicaderma; Endhometrol; Homeoptic; Homeovox; Sedatif PC; Symphytum Complexe No 48†; ***Ger.:*** Arnica Comp; Calendumed; Cefalymphat H†; Cefalymphat†; Infihepan; Lymphdiaral sensitive N; Lymphdiaral; Lymphdiaral; Naranotox comp; Odonton-Echtroplex; Ruta-Gastreu N R55; Traumeel S; Wecesin; Weleda Heilsalbe; ***Hung.:*** Calendumed; Homeovox; Sedatif; Traumeel; ***Neth.:*** Achilite; Calendulan; Calendulan; Dermalite; Homeoptic†; Homeovox; Lymphdiaral; Lymphdiaral; Mercurialis zalf; Omnilite; Sedatif PC; Traumeel H; Traumeel S; Vinceel H; ***Port.:*** Homeodent†; Homeoplasmine†; Homeovox; Sedatif PC; ***Rus.:*** Cicaderma (Цикадерма); Homeostres (Гомеострес); Homeovox (Гомеовокс); Mercure-Plus (Меркур-Плюс); Repisan (Реписан); Traumeel S (Траумель С); Urtica-Plus (Уртика-Плюс); ***S.Afr.:*** Traumeel S; ***Switz.:*** Contusin; Homeoplasmine; Sedatif PC; Traumeel; ***UK:*** Balsamicum; Burns Cream; Haemorrhoid Cream; Healing Cream; Hypercal; Oleum Rhinale; Pyrethrum Spray; WCS Dusting Powder; ***Ukr.:*** Homeovox (Гомеовокс); Sedatif PC (Седатив ПЦ); Traumeel S (Траумель С); ***USA:*** Traumeel; ***Venez.:*** Traumeel.

California Poppy

Californian Poppy; Eschscholtzia; Gold Poppy; Goldmohn; Kaliforniantuliunikko; Kalifornischer Kappenmohn; Pavot de Californie; Schlafmützchen; Sömntuta; Tuliunikko.
ATC Herb — HN05CW5003 (Eschscholzia californica: *herb*).
UNII — 9315HN272X (Eschscholzia californica); *023XWA119J* (Eschscholzia californica *flowering top*).

NOTE. *Eschscholzia californica* was the first named member of the genus *Eschscholzia*, named in honour of the botanist Johann Friedrich von Eschscholtz. It should be noted that the "t" in the personal surname is generally now not included in the scientific botanical name but many sources still spell the genus as *Eschscholtzia* or even as *Escholtzia*.

Pharmacopoeias. In *Fr.*

Profile

The dried aerial parts of the California poppy, *Eschscholzia californica* (Papaveraceae), are used in herbal preparations for anxiety disorders and insomnia.

The herb contains several alkaloids, reported to include cryptopine and protopine.

Homoeopathy

California poppy has been used in homoeopathic medicines under the following names: Eschscholtzia californica; Eschscholtzia.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Austral.*: The Blue One†; *Fr.*: Calmiflorine†; Fibromyalgine Fort; Panxeol†; Phytozac Plenesia; Sedaloziat†; Sedopal; Sympathyl; *Ger.*: Requiesan†; *Ital.*: Alosen†; Dormil; Fisioreve CM; Fitosonno; Vagostabil Junior; *Rus.*: Sympathyl (Симпатил).

Homoeopathic Preparations. *Ger.*: Dormi-Gastreu S R14; *Rus.*: Passidorm (Пассидорм).

Calumba

Calumba Root; Colombo; Raíz de colombo; Калумба.
UNII — V36I288LD5.

Pharmacopoeias. In *Jpn.*

Profile

Calumba, the dried root of *Jateorhiza palmata* (*J. columba*) (Menispermaceae), has been used as a bitter and as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Wunderbalsam; *Switz.*: Padma-Lax; Padmed Laxan; *UK*: Appetiser Mixture; Pegina.

Camostat Mesilate (*pINNM*) ⊗

Camostat, Mésilate de; Camostat, mesilato de; Camostat Mesylate; Camostati Mesilas; FOY-305; Mesilato de camostat; Камостата Мезилат.
N,N-Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)phenylacetate methanesulphonate.
$C_{20}H_{22}N_4O_5,CH_4O_3S$=494.5.
CAS — 59721-28-7 (camostat); 59721-29-8 (camostat mesilate).
ATC — B02AB04.
ATC Vet — QB02AB04.
UNII — 451M50A1EQ.

Pharmacopoeias. In *Jpn.*

Profile

Camostat mesilate is a proteolytic enzyme inhibitor that has been given orally for the treatment of postoperative reflux oesophagitis (see Gastro-oesophageal Reflux Disease, p. 1807.2) in a dose of 100 mg 3 times daily, and for remission of the acute symptoms of chronic pancreatitis (p. 2580.2) in a dose of 200 mg 3 times daily.

References

1. Ashizawa N, *et al.* Efficacy of camostat mesilate compared with famotidine for treatment of functional dyspepsia: is camostat mesilate effective? *J Gastroenterol Hepatol* 2006; 21: 767–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Foipan.

Camphene

Kamfen; Камфен.
2,2-Dimethyl-3-methylenebicyclo[2.2.1]heptane.
$C_{10}H_{16}$=136.2
CAS — 79-92-5.
UNII — G3VG94Z26E.

Profile

Camphene is a constituent of several essential oils. It has antiseptic and antispasmodic actions and is included in preparations for the treatment of biliary- and urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Rowatinex; *Austria*: Rowachol; Rowatinex; *Chile*: Rowatinex; *Cz.*: Rowachol; Rowatinex; *Ger.*: Rowachol; Rowatinex; *Hong Kong*: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; *Hung.*: Rowachol; Rowatinex; *Irl.*: Rowachol; Rowatinex; *Israel*: Rowachol; Rowatinex; *Malaysia*: Rowachol; Rowatinex; *Mex.*: Cholex; *Philipp.*: Rowachol; Rowatinex; *Pol.*: Rowachol; Rowatinex; Terpichol; *Rus.*: Rowatinex (Роватинекс); *Spain*: Rowachol; Rowanefrin; *Thai.*: Rowachol; Rowatinex; *UK*: Rowachol; *Venez.*: Rowachol; Rowatinex.

Camphor

Alcanfor; 2-Camphanone; D-Camphor (natural); Camphora; Camphora D; Camphre; Camphre Droit (natural); Camphre du Japon (natural); Cânfora; D-Kafr; Kafr; Kamfer; Kamferi; Kámfor; Kamfora; Kamparas; Камфора.
Bornan-2-one; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one.
$C_{10}H_{16}O$=152.2
CAS — 76-22-2 (± camphor); 21368-68-3 (± camphor); 464-49-3 (+ camphor); 464-48-2 (- camphor).
ATC — C01EB02.
ATC Vet — QC01EB02.
UNII — 5TJD82A1ET (synthetic DL-camphor); N20HL7Q941 (natural D-camphor).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*; some only describe natural camphor and some only synthetic camphor;

Eur. and *Jpn* have separate monographs for natural and racemic or synthetic camphor.

Ph. Eur. 8: (Camphor, Racemic). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.

Ph. Eur. 8: (D-Camphor; Natural Camphor BP 2014). A white or almost white, crystalline powder or friable crystalline masses, highly volatile even at room temperature. Slightly soluble in water; very soluble in alcohol and in petroleum spirit; very slightly soluble in glycerol; freely soluble in fatty oils.

USP 36: (Camphor). A ketone obtained from *Cinnamomum camphora* (Lauraceae) or produced synthetically. The natural product is dextrorotatory and the synthetic product is optically inactive.

Colourless or white crystals, granules, or crystalline masses, or colourless to white, translucent, tough masses with a penetrating characteristic odour. It slowly volatilises at ordinary temperatures.

Soluble 1 in 800 of water, 1 in 1 of alcohol, 1 in 0.5 of chloroform, and 1 in 1 of ether; freely soluble in carbon disulfide, in petroleum spirit, and in fixed and volatile oils. Store at a temperature not exceeding 40 degrees in airtight containers.

Compounding. A liquid or soft mass is formed when camphor is triturated with chloral hydrate, menthol, phenol, and many other substances. Camphor is readily powdered by triturating with a few drops of alcohol, ether, or chloroform.

Uses and Administration

Applied externally, camphor acts as a rubefacient and mild analgesic (see p. 6.3) and is used in liniments as a counter-irritant in fibrositis, neuralgia, and similar conditions. It is also an ingredient of many inhaled nasal decongestant preparations but it is of doubtful efficacy. The use of camphor liniment (camphorated oil) is discouraged because of its potential toxicity. It has been withdrawn from the market in both the UK and the USA. In the USA the concentration of camphor in preparations for external use may not exceed 11% and use is controlled or limited, particularly in children, in many countries.

Camphor oil is occasionally used in aromatherapy.

Taken internally camphor has irritant and carminative properties and has been used as a mild expectorant. It has also been used in mixed preparations for cardiovascular disorders.

Adverse Effects

In addition to accidental ingestion of preparations containing camphor, poisoning has also occurred after giving camphorated oil (camphor liniment) to children in mistake for castor oil. The symptoms include nausea, vomiting, epigastric pain, headache, dizziness, oropharyngeal burning, delirium, muscle twitching, epileptiform convulsions, depression of the CNS, and coma. Breathing is difficult and the breath has a characteristic odour; anuria may occur. Death from respiratory failure or status epilepticus may occur; fatalities in children have been recorded from 1 g. There have been reports of instant collapse in infants following the local application of camphor to their nostrils.

Effects on the nervous system. Although the use of camphor in medicinal products is controlled in many countries (see under Uses and Administration above), sporadic cases of toxicity continue to be reported.[1] Three cases of seizures in children aged from 15 to 36 months in the USA were associated with imported camphor preparations used as natural remedies or pesticides by some ethnic groups. In 2 of the cases, the camphor-containing preparation was ingested, while the third patient was exposed to toxic concentrations of camphor through repetitive topical application.

1. Khine H, *et al.* A cluster of children with seizures caused by camphor poisoning. *Pediatrics* 2009; 123: 1269–72.

Treatment of Adverse Effects

Supportive care, including anticonvulsant therapy, is the mainstay of treatment of camphor intoxication. The benefits of gastric decontamination are uncertain, but oral activated charcoal, or gastric lavage after potentially life-threatening overdose, may be considered if the patient presents within 1 hour of ingestion; any convulsions must be controlled first. Haemodialysis with a lipid dialysate or haemoperfusion have been tried but are of doubtful value.

Precautions

Camphor should not be applied to the nostrils of infants even in small quantities, as this may cause immediate collapse.

The UK Committee on the Review of Medicines[1] recommended that camphor should not be included in products intended for the treatment of hepatic and biliary disorders, gallstones, colic, renal disorders, urinary-tract infections, or ureteral stones. The use of camphor parenterally or as irrigants was considered undesirable due to the associated safety hazard.

1. Anonymous. Camphorated oil: licensing authority takes action on camphor products. *Pharm J* 1984; 232: 792.

Pharmacokinetics

Camphor is readily absorbed from all administration sites. It is hydroxylated in the liver to yield hydroxycamphor metabolites which are then conjugated with glucuronic acid and excreted in the urine. Camphor crosses the placenta.

For reference to a study on the dermal absorption of camphor, menthol, and methyl salicylate, see Menthol, p. 2554.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Band-Aid Anti-Itch†; Jointflex†; Watkins Liniment†; *Fr.*: Camphrice Du Canada; *Ger.*: Camphoderm N; Korovit Kreislauf; Mulmicor†; Pectocor N; Rheunervol N; Vaopin N†; *India*: Capsigyl-D; *Pol.*: Migrenol†; *Port.*: Vicks Vaporub; *Switz.*: Bronchomed; *UK*: Rohto Zi; *USA*: Benadryl Children's Anti-Itch; Benadryl Children's Itch Cooling.

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

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Sports Ice Joint & Muscle; *Austria*: Schnarchex; *Canad.*: Eczema L87; Soludor†; *Fr.*: Boripharm No 15†; Scabiosa Complexe No 87; Soludor; Strophantus Compose; Vinicard†; *Ger.*: Aktivon; Chamoca M; Conva-cyl Ho-Len-Complex; Corselect N; Corvipas SL; Crataegus comp; Diacard; Grippe-Gastreu S R6; Hevert-Activon Kreislauftropen†; Infi-Camphora; Infifer N; Korolinda; Myonasan; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Procordal; Roth's Rotacard; Santa Flora S; *Neth.*: Calendulan; Grippe-Gastreu R6; Phonix Solidago comp; *Rus.*: Tonginal (Тонгинал); *Switz.*: Gouttes d'Or; *UK*: Catarrh Cream; *Ukr.*: Tonginal (Тонгинал).

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Concentrated Camphor Water; Concentrated Camphorated Opium Tincture;

USP 36: Camphor Spirit; Camphorated Phenol Topical Gel; Flexible Collodion.

Camphor Monobromide

Alcanfor Bromuro; Bromkampfer; Camphor Monobromate; Camphora Monobromata; Camphre Brome; Kamferimonobromaatti; Kamfermonobromat; Monobromated Camphor.
3-Bromocamphor; 3-Bromo-2-bornanone.
$C_{10}H_{15}BrO$=231.1.
CAS — 76-29-9.

Profile

Camphor monobromide was formerly used for its sedative properties, similarly to other bromides (see p. 2460.3). It has also been used in preparations for urinary disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Mictasol Azul; ***Belg.***: Mictasol; ***Braz.***: Mictasol.

Camylofin Hydrochloride *(rINNM)*

Acamylophenine Hydrochloride; Camilofina, hidrocloruro de; Camylofin Dihydrochloride; Camylofine, Chlorhydrate de; Camylofini Hydrochloridum; Hidrocloruro de camilofina; Камилофина Гидрохлорид.
Isopentyl 2-(2-diethylaminoethylamino)-2-phenylacetate dihydrochloride.
$C_{19}H_{32}N_2O_3,2HCl$=393.4
CAS — 54-30-8 (camylofin); 5892-41-1 (camylofin hydrochloride).
ATC — A03AA03.
ATC Vet — QA03AA03.
UNII — MO02H82C7M.

Profile

Camylofin is used as an antispasmodic, usually in combination preparations. It is usually used as the hydrochloride; the noramidopyrine mesilate and the sodium salts have also been used.

Overdosage. Ingestion of large doses of camylofin by 2 infants produced symptoms similar to those of opioid intoxication.[1] Both infants responded to treatment with naloxone.

1. Schvartsman S. *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; ii: 1246.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Anafortan.

Multi-ingredient Preparations. ***Arg.***: Apasmo; ***Austria***: Avamigran; ***Braz.***: Espasmo Silidron; ***India***: Anafortan-N; Anafortan; Anaspas; ***Ukr.***: Nomigren (Номигрен).

Cannabidiol ⊗

CBD; Каннабидиол.
(3*R*, 4*R*)-2-*p*-Mentha-1,8-dien-3-yl-5-pentylresorcinol.
$C_{21}H_{30}O_2$=314.5
CAS — 13956-29-1.
UNII — 19GBJ60SN5.

Profile

Cannabidiol is a cannabinoid present in cannabis (below) that is being used or under investigation for several potential therapeutic uses. For the use of a buccal spray preparation containing cannabis extracts, whose main active ingredients are dronabinol and cannabidiol, (see Nabiximols, p. 2566.3).

For references to the potential uses of cannabidiol, see under Cannabis, p. 2468.1.

Cannabis ⊗

Cáñamo Indiano; Cannab; Cannabis Indica; Chanvre; Hanfkraut; Indian Hemp.
CAS — 8063-14-7.
*ATC Herb — HA04WA5001 (*Cannabis sativa: *herb).*
*UNII — 8X454SZ22D (*Cannabis sativa *subsp.* sativa *flowering top); FT55RM302N (*Cannabis sativa *subsp.* indica *top).*

Description. Cannabis consists of the dried flowering or fruiting tops of the pistillate plant of *Cannabis sativa* (Cannabinaceae). In the UK cannabis is defined by law as any part of any plant of the genus *Cannabis*. *Marihuana* usually refers to a mixture of the leaves and flowering tops. *Bhang, dagga, ganja, kif,* and *maconha* are commonly used in various countries to describe similar preparations. *Hashish* and *charas* are names often applied to the resin, although in some countries *hashish* is applied to any cannabis preparation.

A series of cannabinoids has been extracted from the plant, the most important being Δ^9-tetrahydrocannabinol (dronabinol), Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, cannabinol, and cannabidiol.

Street names. Cannabis and cannabis preparations have also been known by the following names, many of which are 'street names' (see p. vii) or slang names:

30s; 50; 420; 4.20; 4:20; 4/20; Abu-Sufian; Acapulco; Acapulco gold; Acapulco red; Ace; Afgani indica; Afghan; Afghan black; Afghanais; Afi; African; African black; African bush; Airplane; Ait makhlif; Ak-47; Al Green; Al Sharpton; Aliamba; Amsterdam; Anassa; Angola; Angolaise; Anhascha; Arathi; Arathi Highlands; Ashes; Assassin of Youth; Assyuni; Astro turf; Atshitshi; Aunt Mary; Baby; Baby belong; Baby bhang; Babysitter; Bad One; Bad seed; Bale; Bamba; Bambalacha; Bambia; Bammer; Bammies; Bammy; Bangi-Aku; Bango; Bangoo; Bangue; Banji; Bank Head Bud; Banzai Buds; Bar; Barbara Jean; Barn Man; Bash; BC bud; BC budd; BC Kindbud; Beaster; Beat N Sleep; Belyando spruce; Bergspinasie; Bhang; Bhangaku; Bheng; Biff; Bigfoot; Biggy; Birthday Cake; Black; Black bart; Black ganga; Black gold; Black gungi; Black gunion; Black Maria; Black mo; Black moat; Black powder; Black Russian; Blah; Blast; Blaze; Block; Blonde; Blonde hash; Blow; Blowhead; Blowing smoke; Blue de hue; Blue sage; Blue sky blond; Blueberry; Bo; Bob Hope; Bobby Brown; Bo-bo; Bobo bush; Bohd; Boi; Boléia; Bomb; Bombay Black; Bomb-dizzle; Bone; Boo; Boo boo bama; Boom; Bowgma-Chuff; Brass; Bread; Brick; Bristol Brown; Broccoli; Brown; Brown Frown; B-ster; Bubble gum; Bubonic Chronic; Bud; Buda; Buddha; Buddha grass; Buds; Buen; Bueno; Bullyon; Bunk; Burnie; Burrito; Bush; Butt; Butter; Butter flower; Buzzles; Cabbage; Cable; Caca; Caca de Chango; Cam red; Cam trip; Cambodian red; Can; Canadian black; Canamo; Canapa; Canappa; Cangonha; Canhama; Cann; Cannabis tea; Cannacoro; Can-Yac; Carmabis; Caroçuda; Cavite All Star; Cavite All Stars; CDs; Cereal; Cess; Cest; Chamom; Chara; Charas; Charge; Charris; Cheeba; Cheebong; Cheech and Chong; Cheeo; Cheese; Cherno; Chiba chiba; Chicago black; Chicago green; Chillums; Chippie; Chira; Chitari; Chocolate; Chocolate Thai; Choof; Chrin; Christmas bud; Christmas tree; Chro; Chron; Chron Chron; Chronic; Chucky; Chunky; Chur ganja; Churrus; Churus; Chus; Chutras; Chutsao; Citral; Citrol; Clone; Club; Cochornis; Coconut Rabbi; Colarado cocktail; Colas; Coli; Coliflor tostao; Collie Weed; Colombian; Colombo; Columbia; Columbian; Columbus black; Compresses; Cosa; Costo; Crazy weed; Creeper; Creeper Weed; Crippy; Crown Town Brown; Crying weed; Cryppie; Cryptonie; C.S.; Cubes; Culican; Cumming Air; Cung; Curro; Cush; D Nugs; Da-boa; Dacha; Dagga; Dak; Dancouver; Dan K; Dank; Darakte-Bang; Dark; Dawamesk; Deaf; Dew; Diamba; Diambista; Diggidy; Diggity; Dimba; Ding; Dinkie dow; Dirijo; Dirt; Dirt grass; Ditch; Ditch weed; Ditchweed; Dizz; Djamba; Djoma; Do a joint; Doctor Kissinger's Crutch; DoggyNuggz; Doja; Dokka; Dolja; Domestic; Don jem; Don Juan; Dona Juana; Dona Juanita; Donajuanita; Doob; Doobee; Doobie; Dooko; Dope; Doradilla; Dormilona; Doshia; Double zero; Doug; Doug Funnie; Downtown brown; Dozer; Draf; Draf weed; Drag weed; Draw; Dread; Dro; Droski; Drottleneck; Dry high; Dubbe; Dube; Duby; Durban Poison; Durijo; Durog; Durong; Duros; Dustwallow Marsh; Ebenieghber; El Gallo; Electric Puha; Elephant; Elva; Endo; Erva do norte; Erva maligna; Esra; Esrar; Exotics; Fallbrook redhair; Faso; Feeling; Fêmea; Feng Shui inner tam-tam; Fine stuff; Finger; Finger lid; Fininha; Finote; Fir; Fire; Firebush; Firewood; Flack Juice; Flame; Flower; Flower tops; Fokkra; Food; Four twenty; Fraho; Frajo; Friend; Fruit; Fu; Fuma D'Angola; Fumo brabo; Fumo de cabocio; Funk; Funny stuff; Fur; Gage; Gandia; Ganga; Gange; Gangster; Ganj; Ganja; Ganjila; Garaouich; Garawiche; Garbage; Garoarsch; Gash; Gauche butt; Gauge; Gauge butt; Gauja; Gear; Gerp; Ghana; Ghanja; Giggle smoke; Giggle weed; Gnaoui; Goblet of jam; Gold; Gold star; Golden; Golden leaf; Gong; Gongo; Gonj; Good giggles; Good Goods; Good stuff; Goody-goody; Goof; Goof butt; Gorge; Gozah; Grahni Sherdool; Grain; Grand Pants; Gram; Grapefruit Hydro; Grass; Grass brownies; Grasshopper; Grata; Greefe; Green; Green buds; Green Candy; Green cheesy wham; Green Funk; Green Goblin; Green goddess; Green Jesus Love; Green paint; Green Penis; Greens; Greeter; Grefa; Grefer; Greta; Grey shields; Griefo; Griefs; Grifa; Griff; Griffa; Griffa-griffo; Griffo; Grim Creeper; Grimmy; Grolid; Guabza; Guaza; Gunga; Gungeon; Gungun; Gunja; Gunjah; Gunney; Gunney sack; Gunza; Gweeler; H; H caps; Hachiche; Haircut; Hairy Ogre; Hameni; Hamp; Hang Liu; Hanhich; Haouzi; Harm reducer; Harry Potter; Harsh; Has; Hascisc; Hash; Hash oil; Hashish; Hasis; Hasji's; Hasjisj; Haszysz; Hawaiian; Hawaiian Black; Hawiian homegrown hay; Hax; Haxixe; Hay; Haze; Headies; Heady Nugs; Heat; Heloua; Hemp; Hen-Nab; Herb; Herba; Herbals; Herbalz; High; High-Grade; Hippie Lettuce; Hocus; Hola-wola-shupidy-doo; Home Grown; Homegrown; Hooch; Hooda; Hooter; Huile; Humboltd Green; Hursini; Hydro; Hydrophonic; Hyge; Ice Cream; Igbo; Indian boy; Indian hay; Indian hemp; Indiana ditchweed; Indiana hay; Indica; Indische-hennepkruid; Indisk hampa; Indo; Indonesian bud; Indoor; Instaga; Instagu; Intianhamppu; Intsangu; Isangu; Ish; IZM; Jamaican gold; Jamaican red; Jamaican red hair; Jane; Janjah; Janjaweed; Jatiphaladya churna; Jay smoke; Jea; Jive; Jive stick; Johnson grass; Jolly green; Jonko; Joy smoke; Juan Valdez; Juana; Juanita; Juja; Kabak; Kaff; Kajees; Kalakit; Kali; Kamonga; Kanab; Kansas Grass; Karpura rasa; Kate bush; Kawaii electric; Kaya; KB; K.B.; Kee; Keif; Kentucky blue; Key; KGB; K.G.B.; Khanh-Chha; Khanje; Khayf; Khif-kiff; Ki; Kief; Kif; Kif Ktami; Kiff; Kill; Killer; Killer green bud; Killer weed; Kilroy; Kilter; Kind; Kind bud; Kind-Bud; Kine-Bud; King bud; Kinnab; Kitt; Kolto; Kona gold; Kraut; Krippies; Krippy; Kryptonite; Kumba; Kush; Kushempeng; Kutchie; Kynd; Kynd-Bud; La-LaLa; Ladies; Lakbay diva; Lakbay viva; Lamb's bread; Lang; Laughing grass; Laughing weed; Leaf; Lebanese; Lebanese blonde; Lebanese gold; Leno; Leon Mcarthy; Leon Punders; LG; Liamba; Lianda; Light Green; Light stuff; Lima; Limbo; Lime green; Little green friends; Little smoke; L.L.; Llesca; Loaf; Lobo; Local weed; Loco; Loco Weed; Locoweed; Longbottom Leaf; Loose shank; Love nuggets; Love weed; Lows; Lubage; Lucas; Lumber; M; Macaroni; Machinery; Macon; Maconha; Maconia; Madi; Mafu; Maggie; Magic smoke; Magiyam; Majat; Makhlif; Malak; Malawi Cob; Malawi Gold; Malawi grass; Malawian gold; Malva; Manhattan silver; Manitoba Hydro; Manzul; Marachuan; Maraguango; Marajuana; Marie Jeanne; Marie-Jane; Marie-Juana; Marigongo; Marihuana; Marijuana; Marimba; Mariquita; Marley; Maroc; Marocaine; Maruamba; Mary; Mary Ann; Mary Jane; Mary and Johnny; Mary Jonas; Mary Warner; Mary Weaver; Mary-Ann; Mary-Jane; Mary-Jonas; Matekwane; Maui wauie; Maui-wowie; May Ann; Mbanje; Meck; Meconha; Meg; Meggie; Merda; Merde; Mersh; Messorole; Method; Methtical; Mex; Mexican brown; Mexican green; Mexican locoweed; Mexican red; Mezz; Mid-Grade; Middies; Middys; Midies; Mids; Mighty mite; Mint; Misari; Mister Brownstone; M.J.; Mnoana; Mo; M.O.; Modams; Mohasky; Mohasty; Momea; Momeka; Monte; Mooca; Moocah; Mooster; Moota; Mooters; Mootie; Mootos; Mor a grifa; Moragrifa; Moroc; Mota; Motah; Mother; Moto; Mr. Piff; Mu; M.U.; Muggie; Muggle; Muggles; Mulatinha; Mull; Mundyadi vatika; Murphy; Musty Marty; Muta; Mutah; Mutha; Nail; Namba; Nederweed; Nederwiet; Neihe; Nigra; Nordle; Northern lights; N'rama; Ntsangu; Nug; Nugget; Nuggets; Nuggs; Nugglets; Nwonkaka; Oboy; O.J.; Old Toby; Oleo; Olja; Ooh-Wee; Orange Cat; Oregano; Out-Do; Owl; Ozone; Paca lolo; Pack; Pack a bowl; Pakaloco; Pakalolo; Paki black; Pakistani black; Panama cut; Panama gold; Panama red; Pappa C's funky space boots; Parsley; Passa; Pasta; Pasto; Pat; Pétard; Peinka; Penek; Penka; Philip Drummond; Philly blunts; Piff; Pin; Pine; Pito; Pizza; Platters; Plow; Pocket rocket; Pod; Poison; Poke; Poke Smot; Politics; Po-Pa; Porro; Pot; Potlikker; Potten bush; P.R.; Pretendica; Pretendo; Pretinha; Pretties; Pretty Ladies; Puff; Purp; Purple; Purple haze; Purple Urple; Purps; Quarter moon; Queen Ann's lace; Rafe; Rafi; Rafo; Ragweed; Railroad weed; Rainy day woman; Rangood; Rasta Plant; Rasta weed; RB; Red bud; Red cross; Red dirt; Red oil; Red seal; Redge; Reef; Reefer; Reggies; Reggiwegs; Regs; Regular; Relish; Resin; R.G.B.; Riamba; Righteous bush; Rip; RIP; Roacha; Rocky; Rongony; Root; Rope; Rora; Rosa Maria; Rose Maria; Rose Marie; Rose-Marie; Rough stuff; Rube; Rubia; Ruderalis; Rugs; Sabsi; Sadda; Salad; Salt and pepper; Santa Marta; Sasfras; Sativa; Schwag; Schwagg; Schwamp; Scissors; Scraps; Scrapes; Scrub; Seeds; Sen; Sense; Sensemilia; Sensi; Sess; Sezz; Shake; Sheeba; Sheebz; Shit; Shmagma; Shrimp; Shrubs; Shwig; Shwiggity Shwag; Shwag; Shwuggets; Siddhi; Siddi; Sighirma; Sins; Sinse; Sinsemilla; Sizzla; Skunk; Skunkweed; Sky; Smokage; Smoke; Smoke a bowl; Smoke Canada; Smoochywoochypoochy; Snop; Soap bar; Soles; Soñadora; Soruma; Soul Flower; Soussi; Speed boat; Splim; Square mackerel; Stack; Stank; Stank-a-dank; Stash; Stems; Stick; Sticks; Sticky; Sticky Black; Sticky brown; Sticky Icky; Sticky Icky Icky; Stink weed; Stinkweed; Stinky; Stoney weed; Stress; Striijj; Stuff; Subji; Sugar weed; Summitates cannabis; SupaDank; Super grass; Super pot; Supergrass; Suruma; Swag; Swamp Grass; Swazi Gold; SWED; Sweet Leaf; Sweet Lucy; T; Tablete; Tack; Tahgalim; Tai Alon; Taima; Takkouri; Takrouri; Tea; Tedrika; Teloeut; Tempel; Temple; Temple balls; Teriaki; Texas pot; Texas Red; Texas tea; Tex-mex; Thai Sticks; That Shit; THC; The Dank; The Peeping Jesus; The Pig Farmer's laptop; The Shit That Killed Elvis; The Wizard; Thirteen; Thumb; Thump! Thump! Thump!; Tia; Tical; Tijuana; Time; Time Machine's Glory; TJ; Tochi; Toke; Torch; Towels; Transkei; Trauma; Trees;

Triple A; Tronadora; Trupence bag; Turtle; Tustin; Tweed; Tweeds; Twenty Twen Twen; Tweny Bag; Umya; Unotque; Urumogi; Utilities; Vipe; Viper's weed; Wacky Baccy; Wacky Backy; Wacky Tabacky; Wacky terbacky; Wacky tobaccky; Wacky weed; Wag; Wake and Bake; Wasch; Weasel feed; Wee; Weed; Weed tea; Weed tear; Wewe; Whack; Whackatabacky; Wheat; White Rhino; White Russian; White Widow; White-haired lady; Woo blunts; Woodle; Woof; Wooz; Woozie; X; Yaa; Yamba; Yandi; Yarndi; Yeah; Yeh; Yellow submarine; Yen pop; Yerba; Yerhia; Yesca; Yesco; Yeska; Ying; Yoda; Yoruba; Yum Yum; Zacate chino; Zacatecas purple; Zambi; Zani; Zerouali; Ziele konopi indyjskich; Zig Zag man; Zol; Zoot.

Pharmacopoeias. In *Chin.* and *Jpn.*

Uses and Administration

Cannabis contains about 60 cannabinoids of which the main active constituent is Δ^9-tetrahydrocannabinol. Two types of specific endogenous cannabinoid-binding receptors have been identified. CB_1 receptors are distributed throughout the CNS and some peripheral tissues and are involved in modulation of various neurotransmitters, which is thought to be responsible for the clinical effects of cannabinoids. CB_2 receptors are expressed mainly in immune cells and are thought to be involved in modulation of the immune system. Cannabinoid receptor agonists and antagonists have also been identified.

Therapeutic use. Cannabis was formerly used therapeutically as a sedative or narcotic. The cannabinoid Δ^9-tetrahydrocannabinol (dronabinol, p. 1840.1) and a synthetic cannabinol (nabilone, p. 1865.2) are used as antiemetics in patients receiving cancer chemotherapy. Dronabinol is also used to stimulate appetite in HIV patients with cachexia. Nabiximols (p. 2566.3) is a combination of cannabis extracts, whose main active ingredients are dronabinol and cannabidiol (p. 2467.1). It is used as adjunctive treatment for the symptomatic relief of spasticity and neuropathic pain in multiple sclerosis in adults. This same preparation is also used as adjunctive analgesic treatment in adult patients with advanced cancer who have moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Cannabinoids are also being investigated for other potential therapeutic uses, including relief of spasticity in multiple sclerosis, in spinal cord injury, and in various forms of pain, including diabetic neuropathy and other types of neuropathic pain, and pain associated with rheumatoid arthritis. Cannabis reduces intra-ocular pressure and it has been reported to be of benefit in glaucoma. Vaporisation is being investigated as a means of delivering therapeutic doses of cannabinoids.

Abuse. Cannabis is widely abused as a psychoactive agent and has a long history of such use. The amount of Δ^9-tetrahydrocannabinol in cannabis depends on its geographical source. Proportions also differ depending on the form used and have been reported as: 1 to 4% in the leaves and flowering tops, or even up to 15% in some varieties bred for a high yield of cannabinoids (so-called skunk); 5 to 12% in sinsemilla (obtained from unpollinated female plants); 3 to 6% in the dried resin (hashish); and 30 to 50% in hashish oil expressed from the pressed resin. The usual route of abuse is by smoking cigarettes containing the dried leaves and flowering parts of the plant or the more potent dried resin (hashish); inhalation using water pipes or vaporisers are alternative methods. Cannabis is also ingested in cakes or sweets. Less commonly, cannabis extract or hashish oil is injected intravenously.

References to the potential medical uses of cannabis.

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4. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; 64: 1–11.
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8. Rog DJ, *et al.* Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65: 812–19.
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12. Abrams DI, *et al.* Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007; 68: 515–21.
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14. Seamon MJ, *et al.* Medical marijuana and the developing role of the pharmacist. *Am J Health-Syst Pharm* 2007; 64: 1037–44.

Dependence

Prolonged heavy use of cannabis may lead to tolerance and psychological dependence but the existence of physical dependence remains somewhat controversial. Reported withdrawal symptoms have included anorexia, agitation, apprehension, aggression, anxiety, insomnia, irritability, restlessness, fever, sweating, tremor, dysphoria, rhinorrhoea, headache, and nausea.

Symptoms of withdrawal have been reported in neonates born to mothers who used cannabis during pregnancy, and have included jitteriness and tremulousness, crying, and disturbances in sleep and response to light occurring up to 30 days after birth.

References.

1. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction* 2002; 97: 621–32.
2. Budney AJ, Moore BA. Development and consequences of cannabis dependence. *J Clin Pharmacol* 2002; 42(11 suppl): 28S–33S.
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5. Nordstrom BR, Levin FR. Treatment of cannabis use disorders: a review of the literature. *Am J Addict* 2007; 16: 331–42.
6. Budney AJ, *et al.* Marijuana dependence and its treatment. *Addict Sci Clin Pract* 2007; 4: 4–16.
7. Benyamina A, *et al.* Pharmacotherapy and psychotherapy in cannabis withdrawal and dependence. *Expert Rev Neurother* 2008; 8: 479–91.
8. Hasin DS, *et al.* Cannabis withdrawal in the United States: results from NESARC. *J Clin Psychiatry* 2008; 69: 1354–63.
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Adverse Effects, Treatment, and Precautions

Cannabis is widely abused for its psychological effects and the most important psychoactive cannabinoid is Δ^9-tetrahydrocannabinol. The toxicity of cannabis is dose-related and when used recreationally depends to a large extent on the experience of the user and degree of tolerance. The effects may also be affected by CNS depressants taken at the same time.

The psychological effects produced by low doses of cannabis include calmness, euphoria, relaxation, drowsiness, a feeling of well-being, heightened sensory awareness, and alterations in perception of time, space, colour, or sound. Sedation may occur some time later after the initial effects. Anxiety or panic reactions may also occur at low doses.

As the level of intoxication increases, the user may experience feelings of depersonalisation, disorientation, decreased inhibition, altered mood, memory impairment, and difficulty in maintaining attention. Symptoms of heavy intoxication include incoordination, ataxia, skeletal muscle jerks, and slurred speech. Distrust, dysphoria, poor concentration, slowed reaction times, lethargy, and sedation may also occur. Fear, panic attacks in apprehensive patients, hallucinations, and transient paranoia or psychosis have also been reported.

Cannabis additionally affects several physiological body systems and symptoms of intoxication include tachycardia, palpitations, paroxysmal atrial fibrillation, and orthostatic hypotension; life-threatening ventricular tachycardia may occur after large doses. Decrease in intra-ocular pressure, conjunctival injection, cough, dry mouth, increased appetite, and reduced bowel motility have also been reported.

The toxicity of cannabis is increased with intravenous use. Gastrointestinal disturbances have been reported including nausea and vomiting, abdominal pain, and diarrhoea. Other symptoms include headache, rigors, fever, dyspnoea, cardiovascular irregularities, jaundice, shock, disseminated intravascular coagulation, renal impairment, and death.

Ingestion of cannabis by children is potentially fatal. Mydriasis, hypotonia, hyporeflexia, ataxia, hypothermia, tachycardia, respiratory depression, drowsiness, stupor, and coma have been reported.

Chronic use of cannabis has been reported to reduce resistance to infection, produce persistent neurotoxicity, and the carcinogens present in cannabis smoke potentially increase the risk of cancer. However, there is little conclusive evidence for the long-term effects of cannabis.

Cannabis has been presumed to affect driving because of slowed reaction times, effects on cognition, and perceptual alterations, although there is no conclusive evidence to this effect, and it has not been possible to correlate cannabis blood concentration with specific levels of impaired driving performance.

The risks of gastrointestinal decontamination after ingestion of cannabis may outweigh the benefits if the patient is drowsy or agitated. However, activated charcoal has been recommended within one hour of ingestion of a potentially toxic dose. Ipecacuanha given within 30 to 90 minutes of ingestion has been used as an alternative. Treatment of an overdose or acute toxicity following ingestion or inhalation of cannabis products is symptomatic and supportive. Adults often require little more than reassurance as clinical toxicity is rarely serious and recovery usually occurs spontaneously within several hours. Patients should be monitored for 6 hours after intravenous injection of cannabis products. Children should also be observed for 6 hours after ingestion. Agitated patients may require sedation with diazepam; lorazepam or midazolam have also been used. Haloperidol or ziprasidone are alternatives to benzodiazepines.

Reviews.

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2. American Academy of Pediatrics. Marijuana: a continuing concern for pediatricians. *Pediatrics* 1991; 88: 1070–2.
3. Wills S. Cannabis and cocaine. *Pharm J* 1993; 251: 483–5.
4. Hall W, Solowij N. Adverse effects of cannabis. *Lancet* 1998; 352: 1611–16.
5. Ashton CH. Adverse effects of cannabis and cannabinoids. *Br J Anaesth* 1999; 83: 637–49.
6. Ashton CH. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry* 2001; 178: 101–6.
7. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet* 2009; 374: 1383–91.

Breast feeding. The American Academy of Pediatrics deprecates[1] the use of cannabis as a drug of abuse by breast-feeding mothers; a published report[2] indicated that cannabinoids were secreted into breast milk and absorbed by nursing infants, and while no adverse effect was reported to have occurred, some components do have a very long half-life.

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 06/07/04)
2. Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med* 1982; 307: 819–20.

Effects on the cardiovascular system. References.

1. Jones RT. Cardiovascular system effects of marijuana. *J Clin Pharmacol* 2002; 42 (11 suppl): 58S–63S.
2. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol* 2002; 42 (11 suppl): 64S–70S.

Effects on the cerebrovascular system. References.

1. Herning RI, *et al.* Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. *Neurology* 2005; 64: 488–93.

Effects on the CNS. References to, and reviews of, the CNS effects of cannabis, including effects on cognition,[1-5] anxiety and depression,[6] and psychosis,[7-13] including schizophrenia.[14,15] Coma, reversed by flumazenil, has been reported in 2 children who had ingested cannabis.[16]

1. Pope HG Jr, *et al.* Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry* 2001; 58: 909–15.
2. Solowij N, *et al.* Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 2002; 287: 1123–31. Correction: *ibid.*: 1651.
3. Harrison GP Jr, *et al.* Cognitive measures in long-term cannabis users. *J Clin Pharmacol* 2002; 42 (11 suppl): 41S–47S.
4. Gonzalez R, *et al.* Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review. *J Clin Pharmacol* 2002; 42 (11 suppl): 48S–57S.
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6. Patton GC, *et al.* Cannabis use and mental health in young people: cohort study. *BMJ* 2002; 325: 1195–8.
7. McKay DR, Tennant CC. Is the grass greener? The link between cannabis and psychosis. *Med J Aust* 2000; 172: 284–6.
8. Johns A. Psychiatric effects of cannabis. *Br J Psychiatry* 2001; 178: 116–22.
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10. Fergusson DM, *et al.* Cannabis and psychosis. *BMJ* 2006; 332: 172–5.
11. Hall W. Is cannabis use psychotogenic? *Lancet* 2006; 367: 193–5. Correction. *ibid.*: 1056.
12. Moore THM, *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; 370: 319–28.
13. Gonzalez-Pinto A, *et al.* Impact of cannabis and other drugs on age at onset of psychosis. *J Clin Psychiatry* 2008; 69: 1210–16.
14. Zammit S, *et al.* Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* 2002; 325: 1199.
15. Arseneault L, *et al.* Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002; 325: 1212–3.
16. Rubio F, *et al.* Flumazenil for coma reversal in children after cannabis. *Lancet* 1993; 341: 1028–9.

Effects on the eyes. A report of persistent visual abnormalities in a patient after discontinuation of heavy abuse of cannabis.[1] No organic cause for the effects, which were accompanied by less persistent mental changes, could be found.

1. Laffi GL, Safran AB. Persistent visual changes following hashish consumption. *Br J Ophthalmol* 1993; 77: 601–2.

Effects on the gastrointestinal tract. There have been several reports of heavy cannabis use producing recurrent episodes of severe nausea and vomiting accompanied by abdominal pain; the symptoms are temporarily relieved by taking hot baths or showers, which can lead patients into a compulsive bathing habit. The mechanism of action of

this so-called cannabinoid hyperemesis syndrome is unknown. Stopping cannabis use will prevent further episodes but no other treatment is known.

References.
1. Allen JH, *et al.* Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* 2004; 53: 1566–70.
2. Roche E, Foster PN. Cannabinoid hyperemesis: not just a problem in Adelaide Hills. *Gut* 2005; 54: 731.
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8. Sullivan S. Cannabinoid hyperemesis. *Can J Gastroenterol* 2010; 24: 284–5.

Effects on the lungs. References.
1. Tashkin DR, *et al.* Respiratory and immunologic consequences of marijuana smoking. *J Clin Pharmacol* 2002; 42 (11 suppl): 71S–81S.
2. Aldington S, *et al.* Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 2007; 62: 1058–63. Correction. *ibid.* 2008; 63: 385.

Hyperthermia. Life-threatening hyperthermia was reported[1] in a 24-year-old man who went jogging after smoking cannabis.

1. Walter FG, *et al.* Marijuana and hyperthermia. *J Toxicol Clin Toxicol* 1996; 34: 217–21.

Peripheral vascular disease. References.
1. Combemale P, *et al.* Cannabis arteritis. *Br J Dermatol* 2005; 152: 166–9.

Pregnancy. Cannabis has effects on sperm and can alter reproductive hormonal systems. Infants born to mothers exposed to cannabis during pregnancy tend to have a lower birth-weight[1,2] and may suffer from increased excitation in the postnatal period.[3]

1. Zuckerman B, *et al.* Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 1989; 320: 762–8.
2. Frank DA, *et al.* Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *J Pediatr* 1990; 117: 622–6.
3. Silverman S. Interaction of drug-abusing mother, fetus, types of drugs examined in numerous studies. *JAMA* 1989; 261: 1689, 1693.

Interactions

Cannabis and alcohol have additive effects. The sedative effects of cannabis may be potentiated by other CNS depressants. Additive antimuscarinic effects, for example tachycardia, may occur with drugs such as tricyclic antidepressants. Cannabis induces microsomal enzymes and therefore interactions with many drugs that are metabolised by these enzymes might be expected (see, for example, Theophylline, p. 1235.3).

Anticoagulants. For a report of cannabis smoking increasing the effect of warfarin, see p. 1533.2.

Disulfiram. Limited evidence indicates that use of disulfiram with cannabis may produce a hypomanic state.[1]

1. Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* 1983; 140: 243–4.

Pharmacokinetics

Time to onset and duration of effects of cannabis vary with factors such as route of administration and the user's experience. The active principles of cannabis are readily absorbed from the lungs. Systemic bioavailability of Δ^9-tetrahydrocannabinol from smoked cannabis generally ranges between about 10 and 35%, with regular users achieving a higher efficiency. This produces an effect within minutes, reaches a peak in about 30 minutes, and lasts for about 3 to 4 hours. The pharmacokinetics of cannabis after injection are similar to smoking.

Δ^9-Tetrahydrocannabinol absorption may be slow and erratic from the gastrointestinal tract, and extensive first-pass liver metabolism reduces the systemic bioavailability to less than 20% with high interindividual variation. Effects peak in about 1 to 4 hours and last for up to 6 hours.

Δ^9-Tetrahydrocannabinol is lipophilic and becomes widely distributed in the body. Plasma protein binding is about 97 to 99%. Δ^9-Tetrahydrocannabinol is extensively metabolised in the liver via the cytochrome P450 isoenzyme CYP2C subfamily, mainly to the active 11-hydroxy derivative.

Within 72 hours of an oral dose, 10 to 15% is excreted in the urine mainly as conjugates and metabolites, and 35 to 50% in faeces mainly as unconjugated metabolites. About 80 to 90% of a dose is excreted within 5 days after ingestion. Duration of detectability of urinary metabolites varies greatly and can be several weeks for heavy chronic users.

Cannabis crosses the placenta and is distributed into breast milk.

Review.
1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; 42: 327–60.

Canola Oil

Canola, aceite de; Масло Канолы.
CAS — 120962-03-0.
UNII — 331KBJT7RK.

Profile

Canola oil is a form of rapeseed oil (p. 2602.3) from strains selected for low erucic acid content. It is used as an edible oil and in pharmaceutical manufacturing and cosmetics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *NZ*: Mr Nits.

Cantharides

Blistering Beetle; Cantáridas; Cantharis; Insectes Coléoptères Hétéromères; Lytta; Méloïdes; Russian Flies; Spanish Fly; Шпанские Мушки.
UNII — 3Q034RO3BT.

Uses and Administration

Cantharides is the dried beetle *Cantharis vesicatoria* (*Lytta vesicatoria*) (Meloidae) or other spp., containing not less than 0.6% of cantharidin, which is a protective exudate produced by the beetles. The properties of cantharides are those of its active principle, cantharidin (below).

Mylabris (Chinese blistering beetle; Chinese cantharides; Indian blistering beetle), the dried beetles of the species *Mylabrus sidae* (= *M. phalerata*), *M. cichorii*, and *M. pustulator*, has been used as a substitute for cantharides and as a source of cantharidin (see below) in the East.

Homoeopathy

Cantharides has been used in homoeopathic medicines under the following names: Cantharis; Lytta vesicatoria; Canthr.

Adverse Effects

The adverse effects of cantharides are those of its active component, cantharidin, below.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Bladder Irritation; Calendula +; EnurAid; Hylands Formula E; Reneel†; *Fr.*: Amanita Complexe No 75; Cistus Canadensis Complexe No 86†; Geranium Complexe No 108†; Juniperus Complexe No 6; *Ger.*: Cysto-cyl L Ho-Len-Complex; Hewecyst Blasen-Nieren†; Levisticum S; metasolidago S†; Pascorenal-Injektopas; Solidago Hevert Complex; Urofossat; Uroselect; *Neth.*: Opsonat; *Rus.*: Cistoit-GF (Цистоит-ГФ); *S.Afr.*: Berberis/Cantharis Comp†; *Switz.*: Regenaplex Nr 28b; Regenaplex Nr 86a.

Cantharidin

Cantaridina; Кантаридин.
Hexahydro-3aα,7aα-dimethyl-4β,7β-epoxyisobenzofuran-1,3-dione.
$C_{10}H_{12}O_4$=196.2
CAS — 56-25-7.
UNII — IGL471WQ8P.

Uses and Administration

Cantharidin is obtained from cantharides or mylabris (see under Cantharides, above). Cantharidin has vesicant activity and a solution of 0.7% in flexible collodion is applied for the removal of warts and molluscum contagiosum. Preparations of cantharides and cantharidin have also been used externally as rubefacients and counter-irritants. Owing to the intensely irritating nature of cantharidin it should not be taken internally. Also it should not be applied over large surfaces because of the risk of absorption.

Preparations of cantharides and cantharidin were formerly promoted for hair loss but their use in cosmetic products is now prohibited in the UK by law.

Molluscum contagiosum. References.
1. Silverberg NB, *et al.* Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol* 2000; 43: 503–7.
2. Moed L, *et al.* Cantharidin revisited: a blistering defense of an ancient medicine. *Arch Dermatol* 2001; 137: 1357–60.
3. Ross GL, Orchard DC. Combination topical treatment of molluscum contagiosum with cantharidin and imiquimod 5% in children: a case series of 16 patients. *Australas J Dermatol* 2004; 45: 100–2.
4. Hanna D, *et al.* A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol* 2006; 23: 574–9.

Adverse Effects and Treatment

The adverse effects of cantharidin, a protective exudate produced by blistering beetles (see under Cantharides above), are a result of its irritant and vesicant properties and may occur after exposure to preparations of cantharidin or to the beetle itself. Cantharidin produces blistering of mucous membranes. After ingestion of cantharidin there is burning pain in the throat and stomach, difficulty in swallowing, nausea, vomiting, haematemesis, abdominal pain, diarrhoea (sometimes bloody), tenesmus, renal pain, frequent micturition, dysuria, priapism, haematuria, proteinuria, renal failure, severe hypotension, and circulatory failure. Severe gastrointestinal disturbances can produce significant morbidity. Oral doses of cantharidin ranging from 10 to 80 mg have been lethal, although there have been reports of survival after doses up to 175 mg. Cantharidin is lipid soluble and oral bioavailability is increased in the presence of fatty substances.

Dermatological exposure may produce dermatitis, blisters, and ulceration, although symptoms may not appear until several hours later. Significant dermal exposure can give rise to systemic toxicity. Keratoconjunctivitis, iritis, and oedema may result from contact with the eyes or surrounding tissues.

Cantharidin has been abused as a sex stimulant.

Treatment of cantharidin poisoning is largely supportive. Emesis must be avoided following oral ingestion because of the severe irritant effect of cantharidin on mucous membranes. Activated charcoal has been tried, although it is not certain whether it binds to cantharidin.

Poisoning. References.
1. Hundt HKL, *et al.* Post-mortem serum concentration of cantharidin in a fatal case of cantharides poisoning. *Hum Exp Toxicol* 1990; 9: 35–40.
2. Poletini A, *et al.* A fatal case of poisoning with cantharidin. *Forensic Sci Int* 1992; 56: 37–43.
3. Karras DJ, *et al.* Poisoning from "Spanish fly" (cantharidin). *Am J Emerg Med* 1996; 14: 478–83.
4. Tagwireyi D, *et al.* Cantharidin poisoning due to "Blister beetle" ingestion. *Toxicon* 2000; 38: 1865–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Canthacur; Cantharone; *China*: You Si Luo (尤斯洛); *Turk.*: Canthacur.

Multi-ingredient Preparations. *Canad.*: Canthacur-PS; Cantharone Plus; *Turk.*: Canthacur-PS.

Capsicum

Capsic; Capsici fructus; Cayennepfeffer; Chillies; Espanjanpippuri; Paprikų vaisiai; Paprikový plod; Piment de cayenne; Piment Rouge; Pimentão; Red Pepper; Spanischer Pfeffer; Spansk peppar; Перец Красный.
ATC Herb — HM02AB5001 (Capsicum annuum: *fruit*); *HA03AW5006* (Capsicum annuum: *fruit*).
UNII — 6M47G7C4SY (red pepper); T5KDM4J239 (Capsicum *spp. fruit*).

NOTE. Ground cayenne pepper of commerce is normally a blend of varieties of capsicum. Paprika is from *Capsicum annuum* var. *longum*; it is milder than capsicum.

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

Eur. and *US* also include capsicum oleoresin (capsicin).

Ph. Eur. 8: (Capsicum). The dried ripe fruits of *Capsicum annuum* var. *minimum* and small-fruited varieties of *C. frutescens*. It contains a minimum of 0.4% of total capsaicinoids expressed as capsaicin, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Capsicum Oleoresin, Refined and Standardised). A red or brown mobile extract that contains 12.0 to 18.0% of capsaicinoids expressed as capsaicin. It is produced from the herbal drug and alcohol by an appropriate procedure.

Ph. Eur. 8: (Capsicum Soft Extract, Standardised). A reddish-brown glutinous extract that contains 2.0 to 2.4% of capsaicinoids expressed as capsaicin. It is produced from the herbal drug and alcohol by an appropriate procedure.

USP 36: (Capsicum). The dried ripe fruit of various capsicum species. It contains not less than 0.3% of total capsaicinoids, calculated as the sum of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, nonivamide, decanylvanillinamide, and homocapsaicin, and the nonivamide content is not more than 5% of the total capsaicinoids, calculated on the dried basis. During storage, a few drops of chloroform may be added from time to time to prevent attack by insects.

USP 36: (Capsicum Oleoresin). An alcoholic extract of the dried ripe fruits of capsicum. It contains not less than 6.5% of total capsaicinoids, calculated as the sum of capsaicin, dihydrocapsaicin, nordihydrocapsaicin, nonivamide, decanylvanillinamide, and homocapsaicin, calculated on the anhydrous basis. The nonivamide content is not more than 5% of the total capsaicinoids, calculated on the anhydrous basis. It is a powerful irritant, and even in minute quantities produces an intense burning sensation when it comes in contact with the eyes and tender parts of the skin. Contact with the skin and eyes is to be avoided. It is a dark red, oily liquid. Soluble in alcohol, in acetone, in chloroform, in ether, and in volatile oils; soluble with opalescence in fixed oils. Store in airtight containers.

Uses and Administration

Capsicum has a carminative action but it is mainly used externally, often in the form of capsicum oleoresin, as a counter-irritant (see Rubefacients and Topical Analgesia, p. 6.3). It is also included in preparations for the management of cough and cold symptoms. Capsaicin (p. 35.1), the active ingredient of capsicum, is also used in topical preparations in the treatment of painful skin conditions.

Capsicum oleoresin is used in 'pepper sprays' for law enforcement and self defence.

Capsicum also has culinary uses.

Homoeopathy

Capsicum has been used in homoeopathic medicines under the following names: Capsicum annuum; Cap. a.

Adverse Effects

Preparations of capsicum and capsicum oleoresin can be very irritant to the skin and mucous membranes.

Adverse effects of pepper sprays. References to the toxic effects of 'pepper sprays' containing capsicum oleoresin.

1. Brown L, *et al.* Corneal abrasions associated with pepper spray exposure. *Am J Emerg Med* 2000; **18**: 271–2.
2. Zollman TM, *et al.* Clinical effects of oleoresin capsicum (pepper spray) on the human cornea and conjunctiva. *Ophthalmology* 2000; **107**: 2186–9.
3. Chan TC, *et al.* The effect of oleoresin capsicum "pepper" spray inhalation on respiratory function. *J Forensic Sci* 2002; **47**: 299–304.
4. Das S, *et al.* Capsicum spray injury of the eye. *Int Ophthalmol* 2005; **26**: 171–3.
5. Miller JJ, Skolnick J. Inhalation injury after capsaicin exposure. *J Ky Med Assoc* 2006; **104**: 103–5.

Effects on the gastrointestinal tract. The initial response to the ingestion of a hot pepper is a hot or burning sensation in the mouth, which is attributed to the binding of capsaicin to receptors in the oral cavity.[1] Casein-containing substances such as milk can reverse this burning sensation, apparently by displacing capsaicin, this being due to their lipophilicity.

Spicy meals have long been associated with gastrointestinal discomfort and ingestion of meals containing 1.5 g of red or black pepper has been shown to cause signs of gastric mucosal damage comparable with those caused by a 625-mg dose of aspirin.[2] However, other studies in *animals*[3] and humans[4,5] suggest that capsaicin may have a protective effect on gastric mucosa. Ingestion of about 30 g of jalapeño peppers (a capsicum fruit) caused no visible damage to the duodenal or gastric mucosa of 12 healthy subjects[6] and daily ingestion of meals containing a total of 3 g of chilli powder did not affect the clinical progress of patients with duodenal ulcers given antacids.[7]

1. Henkin R. Cooling the burn from hot peppers. *JAMA* 1991; **266**: 2766.
2. Myers BM, *et al.* Effect of red pepper and black pepper on the stomach. *Am J Gastroenterol* 1987; **82**: 211–14.
3. Holzer P. Peppers, capsaicin, and the gastric mucosa. *JAMA* 1989; **261**: 3244–5.
4. Kang JY, *et al.* Chili—protective factor against peptic ulcer? *Dig Dis Sci* 1995; **40**: 576–9.
5. Yeoh KG, *et al.* Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Dig Dis Sci* 1995; **40**: 580–3.
6. Graham DY, *et al.* Spicy food and the stomach: evaluation by videoendoscopy. *JAMA* 1988; **260**: 3473–5.
7. Kumar N, *et al.* Do chillies influence healing of duodenal ulcer? *BMJ* 1984; **288**: 1803–4.

Poisoning. References.

1. Snyman T, *et al.* A fatal case of pepper poisoning. *Forensic Sci Int* 2001; **124**: 43–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Hansaplast ABC Warme-Pflaster; *Braz.*: Hercap; *Chile*: Dolorub Capsico; Parche Leon Fortificante†; *China*: Haojishi (Warm) (好及施 (温感)); *Denm.*: Termo; *Ger.*: Advel†; Capsamol; Dolobene Hot; Finalgon CPD; Rheumamed; Thermo Burger; *Gr.*: Hansaplast Leontos†; *India*: Capsigyl-D; Capsola Medi; *Irl.*: Elastoplast; *Israel*: Dragon Plaster; *Ital.*: Thermogene; *Port.*: Neodor; *Spain*: Alacapsin; Ipsodol; Katrum; Sor Virginia; *Swed.*: Termo; *Switz.*: Hansaplast ABC; *UK*: Fiery Jack; *USA*: Salonpas Hot.

Multi-ingredient Preparations. *Arg.*: Bifena; Sebulex; Veracolate†; *Austral.*: Airborne Immunity; Euphrasia Complex; Euphrasia Compound; For Peripheral Circulation Herbal Plus Formula 5†; Goanna Heat Cream; GR² Control Thermogenic Enhancer; Joint Mobility†; Masculine Herbal Complex; Metabolift Fat Burner; Metabolism Advantage; Osteo-Relief; Percutane†; The Blue One†; *Austria*: Trauma-Salbe warmend; *Belg.*: Rado-Salil; Stilene; Thermocream; *Braz.*: Capilos; Pilulas Ross; *Canad.*: Absorbine Arthritis†; Hot Stuff†; Le Baume Ehrlich†; Natraway Sport 3†; Saw Palmetto Formula†; *Chile*: Cellenergy; *Fr.*: Baume Saint-Bernard; Curomal; Geldolor; Tigre de Chine; *Ger.*: Gothaplast Rheumamed AC†; *Hong Kong*: Salonsip Hot Patch†; Sloan's Liniment†; *India*: Agile; Algipan; Capsigyl-D; Capsigyl; Capsitop; Capsola Plus; Cartigen; Flexi-muv†; Inflazone; Micronac; Myolaxin; Pane Free; Relaxyl; *Indon.*: Lafalos Plus; Osteor-C; Sloan's Liniment†; *Irl.*: Menthol & Wintergreen; Ralgex; *Israel*: Dragon Massage Cream; Ment-O-Cap†; Radian-B; Rublex Massage Cream; *Ital.*: Altadrine; Capso; Capsolin; Criotonal; Gefion; Gelovis; Sloan†; Valcap; Vasotonal; Wasotonal†; *Mex.*: Parche Negro Belladona; *Neth.*: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; *Pol.*: Kapsiplast; *Port.*: Balsamo Analgesico Sanitas; Medalginan; *Rus.*: Efcamon (Эфкамон); Espol (Эспол); Percamf (Перкамф); *S.Afr.*: Brooklax Pills†; Infrarub†; Moultons Pain Paint†; Muscle Rub†; SB 3 Triple Action Pills†; SB Shisalene†; Sloan's Heat Rub; Sloan's Liniment Rub†; Tandpyndruppelst; *Singapore*: Lafalos Plus; *Spain*: Dolokey†; Embrocacion Gras†; Linimento Naion; Termosan; *Thai.*: Carminative Patar; Carminative Sahakarn; Flataco; Flatulence†; Meloids; Mist Carminative; Patarcolate; Patarsul; Veracolate†; *Turk.*: Algo-Wax; Capsalgine; Capsi-Gel; Gelocaps; *UK*: Allens Dry Tickly Cough; Balmosa; Buttercup Syrup; Catarrh Mixture; Cremalgin†; Fiery Jack; Hactos; Hansaplast Herbal Heat Plaster; Herbal Indigestion Naturtabs; Honey & Molasses; Indian Brandee; Indian Brandee; Indigestion and Flatulence; Indigestion Relief; Jamaican Sarsaparilla; Kilkof; Life Drops; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Radian-B; Ralgex†; Rheumatic Pain Relief; Sanderson's Throat Specific; Sanderson's Throat Specific; Vegetable Cough Remover; *Ukr.*: Bronchial Balsam Bells (Бронхиальный Бальзам Белис); Liponorm (Липонорм); *USA*: Adrenoid; Duraflex Comfort; Pharmacists Creme; Pharmacists Lotion; Salonpas Gel Patch Hot; Throat Discs; Xoten-C; *Venez.*: Ehrlich Balsamo.

Homoeopathic Preparations. *Austral.*: Sleep & Insomnia Relief; *Austria*: Berberis Cosmoplex†; Otodolor; Otovowen; Robinia Med Complex; *Canad.*: Capsicum + Arthri-Cream; Earache; Kids' Earache; *Fr.*: Euphrasia Complexe No 115; Grindelia Complexe No 58; Silmum†; *Ger.*: Otovowen; Tonsipret; *Neth.*: Oteel H; Ricura; *Rus.*: Capsicum-Plus (Капсикум-Плюс); Tonsipret (Тонзипрет); *Switz.*: Regenaplex Nr. 24b; *Ukr.*: Incena (Инцена); Tonsipret (Тонзипрет).

Pharmacopoeial Preparations

Ph. Eur.: Capsicum Tincture, Standardised.

Caraway

Alcarahueya; Alcaravea; Alcaravia; Caraway Fruit; Caraway Seed; Carum; Carvi; Carvi fructus; Carvia; Cumin des Prés; Fructus Carvi; Frutos de la alcaravea; Kminový plod; Kmynų vaisiai; Köménytermés; Kumina; Kümmel; Kummin; Owoc kminku; Тмин.

ATC Herb — HA03AW5008 (Carum carvi: fruit).
UNII — W2FH8O28BE

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

Ph. Eur. 8: (Caraway Fruit; Caraway BP 2014). The whole, dried fruits of *Carum carvi*. It contains not less than 3.0% v/w of essential oil, calculated with reference to the dried drug. It has an odour reminiscent of carvone. Protect from light.

The BP 2014 directs that when Powdered Caraway is prescribed or demanded, material containing not less than 2.5% v/w of essential oil shall be dispensed or supplied.

USNF 31: (Caraway). The dried, ripe fruit of *Carum carvi* (Apiaceae). Preserve against attack by insects.

Profile

Caraway is an aromatic carminative, and is used in gastrointestinal disorders and as a flavour. The seeds have culinary uses. It is the source of caraway oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Iberogast; Mag Kottas Krauterexpress Abfuhrtee; Midro Tee; Montana; *Braz.*: Balsamo Branco; *Canad.*: Anti Dyspepsia Digestive Aid†; Clear Capsules†; Formula T4†; *Cz.*: Iberogast; *Fr.*: Santane C_4†; Santane D_5†; Santane F_{10}†; Santane O1; Santane O1; *Ger.*: Carminativum Hofmann†; Carminativum-Hetterich; Floradix Multipretten N; Iberogast; Iberomint†; Montana N; Pascoventral; *Hung.*: Iberogast; Montana; Salus Multipretten; *India*: Bonnispaz; Coliwell; *Israel*: Jungborn†; Lido Tea†; Midro-Tea; *Ital.*: Cadifen; Cadimint; Florelax; Midro; Relaxcol; *Neth.*: Iberogast; *Pol.*: Apinorm†; Iberogast; Laxantol†; Melis-Tonic; Normosan†; Rhelax; Tabletki Przeciw Niestrawnosci; Tabulettae Laxantes; *Rus.*: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные)†; Herbion Drops for the Stomach (Гербион Желудочные Капли †; Kliophyt (Клиофит); *S.Afr.*: Clairo†; *Spain*: Iberogast; *Swed.*: Alpenkraft; Iberogast; Multipretten; *Switz.*: Kernosan Heidelberger Poudre; Tisane favorisant l'allaitement; *Ukr.*: Bon-Ape it (Бон-Аппетит); Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Iberogast (Иберогаст).

Homoeopathic Preparations. *Canad.*: Cynara Complex†; *U.S.*: Laxadoron.

Pharmacopoeial Preparations

USNF 31: Compound Cardamom Tincture.

Caraway Oil

Alcaravea, aceite esencial de; Carvi aetheroleum; Carvi Etheroleum; Carvi, huile essentielle de; Kminová silice; Kuminaöljy; Kümmelöl; Kumminolja; Olejek kminkowy; Oleum Cari; Oleum Carui; Oleum Carvi; Тминное Масло.

ATC Herb — HA03AW5007 (Carum carvi: essential oil).
UNII — C2J9B08Q3I.

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

Ph. Eur. 8: (Caraway Oil). The oil obtained by steam distillation from the dry fruits of *Carum carvi*. A clear colourless or yellow liquid. Relative density 0.904 to 0.920. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Caraway Oil). The volatile oil distilled from caraway. It contains not more than 50% v/v of carvone ($C_{10}H_{14}O$). Soluble 1 in 8 of alcohol (80%). Store in airtight containers. Protect from light.

Profile

Caraway oil is an aromatic carminative and is used in gastrointestinal disorders and as a flavour. It is also employed as caraway water for infant colic (see Gastrointestinal Spasm, p. 1807.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Balyfen†.

Multi-ingredient Preparations. *Austria*: Parodontax†; Sigman-Haustropfen; Spasmo Claim†; *Ger.*: Enteroplant; Floradix Multipretten N; Gastrysat†; Verdauungstropfen Gastrofunkten†; *Hung.*: Enteroplant†; Salus Multipretten; Stompax; *India*: Aniwel DPS; Aquadil-P; Bestozyme P; Bestozyme; Catalyd; Catazyme; Dorzy DPS; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Merozyme-C; Neopeptine; Vitazyme; *Ital.*: Relaxcol; *Mex.*: Enterokan; *Singapore*: Enterokan; *Swed.*: Multipretten; *Switz.*: Flatulex; Huile Po-Ho A. Vogel; *Thai.*: Corinap; Gas-Nep; Gripe Mixture; *UK*: Atkinson & Barker's Gripe Mixture; Nurse Harvey's Gripe Mixture.

Pharmacopoeial Preparations

BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture.

Carbon-13

Carbone 13; Углерод-13.

CAS — 14762-74-4

Profile

Carbon-13 is a naturally occurring, non-radioactive, stable isotope of carbon. It has been used to label organic compounds, such as urea (p. 1727.3), for use in diagnostic tests, including breath tests for the diagnosis of *Helicobacter pylori* infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Pylobactell; *Denm.*: Diabact UBT; Helicobacter Test†; *Fin.*: Diabact UBT; *Fr.*: Hell-Kit; Ubit†; *Ger.*: Diabact UBT; Helicobacter Test; *Gr.*: Helicobacter Test; Pylobactell; *Irl.*: Diabact UBT; *Israel*: C13-Urea; *Ital.*: Breathquality-UBT; Citredici UBT Kit; Expirobacter; Helicokit; *Neth.*: Helico State; Pylobactell; UBTest†; *Norw.*: Diabact UBT; *Pol.*: Pylobactell; *Port.*: Helico-teste; Helicobacter Test; Pylobactell; Ubit; *Spain*: Tau Kit; Ubtest; *Swed.*: Diabact UBT; *Switz.*: Helicobacter Test; Pylori 13; *UK*: Diabact UBT; Pylobactell; *USA*: Meretek UBT.

Multi-ingredient Preparations. *Irl.*: Helicobacter Test; Pylobactell; *USA*: Ez-HBT.

Pharmacopoeial Preparations

USP 36: Urea C 13 for Oral Solution.

Cardamom

Cardamomi; Cardamomo, fruto del; Кардамон.
UNII — 8BC4CUT4JL.

Pharmacopoeias. In *Br.* and *Jpn.* Also in *USNF.*

BP 2014: (Cardamom Fruit). The dried, nearly ripe fruit of *Elettaria cardamomum* var. *minuscula*. Only the seeds are used in making preparations of cardamom and they are used immediately after removal from the fruit. The seeds should not be stored after removal from the fruit. They have a strongly aromatic odour and taste and contain not less than 4% v/w of volatile oil.

USNF 31: (Cardamom Seed). The dried ripe seed of *Elettaria cardamomum* (Zingiberaceae), recently removed from the capsule. Preserve against attack by insects.

Profile

Preparations of cardamom are used as carminatives and as flavours. The seeds have culinary uses. Cardamom seeds are the source of cardamom oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Peritone; *Austria*: Klosterfrau Melissengeist; Mariazeller; *Cz.*: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; *Fr.*: Dida; *Ger.*: Gallexier; Klosterfrau Melissengeist; Montana N; Schwedentrunk Elixier; *Hung.*: Klosterfrau Melisana; *India*: Abana; Manix; Paedritone; *Malaysia*: Bonnisan; *Pol.*: Melisana Klosterfrau; Padma 28; *Rus.*: Sodecor (Содекор); Suprima-Broncho (Суприма-бронхо); *S. Afr.*: Alma†; Enterodyne†; Helmontskruie†; *Switz.*: Arteria-vita; Padma Digestin; Stomacine; *Thai.*: Carminative Patar; Carminative Sahakarn; Caryopin; Mist Carminative; *UK*: Indian Brandee; Padma Circosan; Pegina; *Ukr.*: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†.

Pharmacopoeial Preparations
USNF 31: Compound Cardamom Tincture.

Cardamom Oil

Cardamomo, aceite esencial de; Ol. Cardamom; Кардамоновое Масло.
ATC Herb — HA03AW5024 (Elettaria cardamomum: *essential oil*).
UNII — JM0KJ091HZ.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Cardamom Oil). A clear, colourless or pale yellow liquid, visibly free from water, with an odour of cardamom fruit. It is distilled from crushed cardamom fruit. At 20 degrees it is soluble 1 in 6 of alcohol (70%). Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

USNF 31: (Cardamom Oil). The volatile oil obtained from cardamom seed. Soluble 1 in 5 of alcohol (70%). Store in airtight containers. Protect from light.

Profile

Preparations of cardamom oil are used as carminatives and as flavours.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Aromadigest†; *India*: Aniwel DPS; Aquadil-P; Carmicide; Catalyd; Catazyme; Digeplex; Dorzy DPS; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Vitazyme; *Thai.*: Corinap; Gas-Nep.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Compound Rhubarb Tincture.

Carglumic Acid *(USAN, rINN)*

Acido Carglúmico; Acido carglumico; Acidum Carglumicum; Carglutamic Acid; Karglumik Asit; OE-312; Карглумовая Кислота.
N-Carbamoyl-L-glutamic acid.
$C_6H_{10}N_2O_5$=190.2
CAS — 1188-38-1.
ATC — A16AA05.
ATC Vet — QA16AA05.
UNII — 5L0HB4V1EW.

Profile

Carglumic acid is used for the treatment of hyperammonaemia in patients with *N*-acetylglutamate synthase deficiency. The initial oral dose ranges from 100 to 250 mg/kg daily, adjusted thereafter to maintain normal plasma levels of ammonia. Individual responsiveness to carglumic acid should be tested before starting long-term therapy; daily maintenance doses range from 10 to 100 mg/kg. The total daily dose should preferably be taken as 2 to 4 divided doses before food.

References to the use of carglumic acid in the management of hyperammonaemia due to *N*-acetylglutamate synthase deficiency.

1. Bélanger-Quintana A, *et al.* Hyperammonaemia as a cause of psychosis in an adolescent. *Eur J Pediatr* 2003; 162: 773–5.
2. Caldovic L, *et al.* Restoration of ureagenesis in N-acetylglutamate synthase deficiency by N-carbamylglutamate. *J Pediatr* 2004; 145: 552–4.
3. Gebhardt B, *et al.* N-carbamylglutamate protects patients with decompensated propionic aciduria from hyperammonaemia. *J Inherit Metab Dis* 2005; 28: 241–4.
4. Guffon N, *et al.* Neonatal hyperammonemia: the N-carbamoyl-L-glutamic acid test. *J Pediatr* 2005; 147: 260–2.
5. Jones S, *et al.* N-Carbamylglutamate for neonatal hyperammonaemia in propionic acidaemia. *J Inherit Metab Dis* 2008. Available at: doi: 10.1007/s10545-008-0777-1

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Carbaglu; *Belg.*: Carbaglu; *Cz.*: Carbaglu; *Denm.*: Carbaglu; *Fr.*: Carbaglu; *Ger.*: Carbaglu; *Gr.*: Carbaglu; *Irl.*: Carbaglu; *Israel*: Carbaglu; *Ital.*: Carbaglu; *Neth.*: Carbaglu; *Pol.*: Carbaglu; *Port.*: Carbaglu; *Spain*: Carbaglu; *Swed.*: Carbaglu; *UK*: Carbaglu; *USA*: Carbaglu.

Caroverine *(pINN)*

Caroverina; Carovérine; Caroverinum; Кароверин.
1-[2-(Diethylamino)ethyl]-3-(*p*-methoxybenzyl)-2(1*H*)-quinoxalinone.
$C_{22}H_{27}N_3O_2$=365.5
CAS — 23465-76-1.
ATC — A03AX11.
ATC Vet — QA03AX11.
UNII — XJ73B0K6KB.

Profile

Caroverine is a smooth muscle relaxant with calcium-channel blocking and glutamate-antagonist properties. It is used as the base or the hydrochloride in conditions associated with painful smooth muscle spasm. Typical oral doses (expressed as the base) are 20 to 40 mg three or four times daily. It may also be given by slow intravenous or intramuscular injection in doses of 40 to 80 mg. Caroverine has also been given rectally. It is also used in cerebral circulatory disorders and in tinnitus.

References.

1. Denk DM, *et al.* Caroverine in tinnitus treatment: a placebo-controlled blind study. *Acta Otolaryngol* 1997; 117: 825–30.
2. Ehrenberger K. Clinical experience with caroverine in inner ear diseases. *Adv Otorhinolaryngol* 2002; 59: 156–62.
3. Quint C, *et al.* The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol* 2002; 122: 877–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Delirex†; Spasmium; Tinnitin.

Carqueja

Baccharis.

NOTE. The name carqueja has also been applied to the unrelated plant *Krameria tomentosa* (Krameriaceae).

Profile

Carqueja consists of the aerial stems of several *Baccharis* species (Asteraceae), particularly *B. articulata* and *B. genistelloides* var. *trimera* (*B. trimera*).

Carqueja is used in traditional medicine in South America and is included in herbal remedies mainly for gastrointestinal and hepatic disorders.

Homoeopathy

Carqueja has been used in homoeopathic medicines under the following names: Baccharis trimera.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Alcachofa Plus; Boldina; Digenat; HDG; Hepacur; Hepatodirectol; Radicura; Sabelin; *Braz.*: Gotas Preciosas.

Homoeopathic Preparations. *Fr.*: Poconeol no 37; Poconeol no 74†.

Cartilage and Cartilage Extracts

Хрящ и Хрящевые Экстракты.
UNII — D5P3K3V822 (autologous cultured chondrocytes).

Profile

Preparations containing cartilage or cartilage extracts from various sources have been used in musculoskeletal and joint disorders and as nutritional supplements. Autologous cultured chondrocytes are used for the repair of symptomatic cartilage defects of the femoral condyle in the knee. A product derived from shark cartilage (AE-941, p. 735.3) is under investigation as an antineoplastic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Car-ti-buron; Cartilago Vital; Cartimax; CT1000; *Austral.*: Cartilag†; PM Cartisak; *Austria*: ChondroCelect; *Belg.*: ChondroCelect; *Cz.*: ChondroCelect; *Indon.*: Fellafit; Sharko Inside; *Irl.*: ChondroCelect; *Pol.*: ChondroCelect; *Port.*: ChondroCelect; *Spain*: ChondroCelect.

Multi-ingredient Preparations. *Arg.*: Car-ti-buron Flex; Cartiflex; Collagen T2-Gag; Rep-Cartil; *Chile*: Cartilago T-500†; Rumalon; *Fr.*: Captafer; Corvitec; *Mex.*: Mex-Amina; *Rus.*: Rumalon (Румалон); *S.Afr.*: Zeel; Zeel; *Thai.*: Cal-ups Join.

Homoeopathic Preparations. *Cz.*: Zeel Salbe†; *Ger.*: NeyArthros Nr 43-Sol†; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyAthos Nr 43; *Hung.*: Zeel; *Rus.*: Zeel T (Цель Т).

Oriental Cashew

Anacardier d'orient; Anacardium; Cashew-pähkinä; Indisk nöt; Marking Nut Tree; Markingnut Tree; Nanercz wschodni; Semecarpus anacardium; Восточный Анакардовый Орех.
UNII — Y0F0BU8RDU (Semecarpus anacardium *juice*); *1SNJ70152E* (Semecarpus anacardium).

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Oriental Cashew for Homoeopathic Preparations; Semecarpus Anacardium ad Praeparationes Homoeopathicas). The dried fruit of *Semecarpus anacardium* (*Anacardium orientale*). It contains a minimum 6.0% of total phenol derivatives expressed as eugenol.

Profile

Various parts of the oriental cashew, *Semecarpus anacardium* (Anacardiaceae), and their preparations are used in traditional Indian medicine. The oil contains bhilawanols, irritant substances reputed to have cytotoxic action.

Homoeopathy

The dried ripe fruit of oriental cashew is used in homoeopathic medicines under the following names: Anacardium; Semecarpus anacardium; Anacardium orientale; Anacard or; Anac. or.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Astomera; *Canad.*: Barijodeel†; Formula ES 211; Nervita; *Chile*: Anacardio con Fosforo; Bioactiv M; *Fr.*: Abbe Chaupitre no 6; Acidum Phosphoricum Compose†; Anxietum; Euphorbium Complexe No 88; *Ger.*: Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Lowe-Komplex Nr 6; Mucosa compositum; Nervoid N; Rytesthin; Sedaphin†; Stoma-Gastreu S R5; Ventrigutt M; *Hung.*: PSY-Stabil; *Neth.*: Cerebrum comp; Emvita 7; Mucosa comp H; Nervofleur; PSY-stabil; *Rus.*: Анабар (Анабар); *Switz.*: Regenaplex Nr. 25a.

Cassia Oil

Aceite de Casia; Canela de la China, aceite de; Cannelier, huile essentielle de; Cassiaöl; Chinese Cinnamon Oil; Cinnamomi Cassiae Aetheroleum; Cinnamomi Cassiae Ethéroleum; Kassiakaneliöljy; Kassiaolja; Kínai fahéjolaj; Kininių cinamonų eterinis aliejus; Oleum Cassiae; Oleum Cinnamomi; Oleum Cinnamomi Cassiae; Silice skořicovníku čínského; Масло Кассии.
UNII — A4WO0626TS.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia*. However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia*. Care should be taken to differentiate between the botanical sources.

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

Chin. P. under the title of Oleum Cinnamomi specifies oil from *Cinnamomum cassia*. *JpnP.* under the title Cinnamon Oil

allows oil from either *C. cassia* or from *C. zeylanicum* [*C. verum*].

Chin. and *Jpn* also include bark (cassia bark) from *Cinnamomum cassia* although the titles are Cortex Cinnamomi and Cinnamon Bark respectively.

Ph. Eur. 8: (Cassia Oil). The oil obtained by steam distillation of the leaves and young branches of *Cinnamomum cassia* (*C. aromaticum*). It contains 70 to 90% of cinnamaldehyde. A clear, mobile, yellow to reddish-brown liquid, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from heat.

Profile

Cassia oil, obtained from *Cinnamomum cassia*, has properties resembling those of cinnamon oil (p. 2479.3) and is used similarly as a carminative and flavour. It has also been used in aromatherapy. Hypersensitivity to cinnamaldehyde, the main constituent of cassia oil, has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Tiger Balm Red; *Cz.*: Klosterfrau Melisana; *Hung.*: Klosterfrau Melisana; *India*: Abana; Diakof; Himcolin; Kofarest-H; Koflet; *Malaysia*: Shine Maxtra; *Rus.*: Sodecor (Содекор); *S.Afr.*: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Entressdruppels HM; Moultons Pain Paint†; Stuidruppels; *UK*: Dragon Balm; *Ukr.*: Bronchomed (Бронхомед); Huato Pills (Болюсы Хуато).

Castor

Castoreum.

Profile

Castor is the dried scent-glands (preputial follicles) of the beaver, *Castor fiber* and *Castor canadensis*. It has been used in perfumery.

Homoeopathy

Castor has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Bano Svedkeseru; *Ukr.*: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Castor Oil

Aceite de Ricino; Hintyağı; Huile de Ricin; Ol. Ricin.; Oleum Ricini; Ricini Oleum; Ricini Oleum Virginale; Ricino, aceite de; Ricinolja (Jungfruolja); Ricinový olej panenský; Ricinusolaj; Risiinilöljy, neitsytöljy; Rizinusöl; Клещевинное Масло; Касторка; Касторовое Масло.

ATC — A06AB05.

ATC Vet — QA06AB05.

ATC Herb — HD02WB5010 (Ricinus communis: oil); HS01XW5001 (Ricinus communis: oil); HA06AB5016 (Ricinus communis: oil).

UNII — D5340Y219G.

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

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

Eur. also includes hydrogenated castor oil and refined castor oil. *USNF* includes hydrogenated castor oil.

Ph. Eur. 8: (Castor Oil, Virgin). The fatty oil obtained by cold expression from the seeds of *Ricinus communis*. During the expression step the temperature of the oil must not exceed 50 degrees. A suitable antoxidant may be added. Relative density about 0.958. It is a clear, at 40 degrees, slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled airtight containers. Protect from light.

Ph. Eur. 8: (Castor Oil, Hydrogenated; Ricini Oleum Hydrogenatum). The oil obtained by hydrogenation of castor oil. It consists mainly of the triglyceride of 12-hydroxystearic acid. Almost white to pale yellow fine powder, masses, or flakes. M.p. 83 degrees to 88 degrees. Practically insoluble in water and in petroleum spirit; very slightly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Store in well-filled containers.

Ph. Eur. 8: (Castor Oil, Refined). The fatty oil obtained by cold expression from the seeds of *Ricinus communis* and then refined. A suitable antoxidant may be added. Relative density about 0.958. It is a clear, almost colourless or slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit. Store in well-filled, airtight containers. Protect from light.

USP 36: (Castor Oil). The fixed oil obtained from the seed of *Ricinus communis* (Euphorbiaceae). It is a pale yellowish or almost colourless, transparent, viscid liquid. Has a faint, mild odour; is free from foreign and rancid odour; and has a bland, characteristic taste. Soluble in alcohol; miscible with dehydrated alcohol, with chloroform, with ether, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40 degrees.

USNF 31: (Hydrogenated Castor Oil). Refined, bleached, hydrogenated, and deodorised castor oil, consisting mainly of the triglyceride of hydroxystearic acid. A white, crystalline wax. M.p. 85 degrees to 88 degrees. Insoluble in water and in most common organic solvents. Store in airtight containers at a temperature not exceeding 40 degrees.

Uses and Administration

Castor oil is used externally for its emollient effect. It has also been used topically to allay irritation due to foreign bodies in the eye. Castor oil may be used as a solvent in some injections, and as a plasticiser.

Hydrogenated castor oil is used as a stiffening agent. Polyoxyl castor oils (p. 2202.3) are used as emulsifying and solubilising agents.

Castor oil has been used as a laxative, but such use is obsolete.

Adverse Effects and Precautions

Oral administration of castor oil, particularly in large doses, may produce nausea, vomiting, colic, and severe purgation. Castor oil should not be given when intestinal obstruction is present.

The seeds of *Ricinus communis* contain a toxic protein, ricin (p. 2604.2). Allergic reactions have been reported in subjects handling the seeds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Laxol; *Ger.*: Laxopol†; *Israel*: Laxopol; *Mex.*: Ricitel†; *Switz.*: Rical; *Turk.*: Ricilaks; Riciment; Ricipan; *USA*: Emulsoil; Neoloid†.

Multi-ingredient Preparations. *Canad.*: Refresh Ultra; *Chile*: Node DS†; *Cz.*: Suspensio Visnevski cum Pice Liquida HBF; *Ger.*: Itax†; *India*: Coliwell; *Pol.*: Salicylol; *Rus.*: Urocholesan (Урохолесан); Urolesan (Уролесан); *Spain*: Callicida Cor Plk†; Keranin†; Linitul; Otocerum; *Switz.*: Peru Stick; *Ukr.*: Urolesan (Уролесан); *USA*: Allanderm-T†; Boudreaux's All Natural Butt Paste; Boudreaux's Butt Paste; Dermuspray; Dr Dermi-Heal; Granulderm†; Granulex; GranuMed; Mammol; Optase; Proderm; Vasolex; Venelex; Xenaderm.

Homoeopathic Preparations. *Switz.*: Silacten.

Pharmacopoeial Preparations

BP 2014: Chloroxylenol Solution; Flexible Collodion; Zinc and Castor Oil Ointment;

USP 36: Aromatic Castor Oil; Castor Oil Capsules; Castor Oil Emulsion; Flexible Collodion.

Catalase

Caperase; Catalasa; EC 1.11.1.6; Equilase; Optidase; Каталаза.

CAS — 9001-05-2.

Profile

Catalase is an enzyme obtained from many biological sources including animal liver (hepatocatalase) and certain bacteria and fungi. It is a protein composed of 4 polypeptide subunits, the precise composition of which varies according to the source, and has a molecular weight of about 240 000. Catalase has the ability to promote the decomposition of hydrogen peroxide to water and oxygen.

It has been applied to wounds and skin ulcers and has also been used in the treatment of vitiligo. It has sometimes been used with glucose oxidase (p. 2516.3) in food preservation to break down hydrogen peroxide produced during oxidation of glucose, and is also included in preparations for contact lens care to neutralise hydrogen peroxide.

Catalase is a free-radical scavenger and has been investigated for its ability to limit reperfusion injury thought to be related to free-radical production. Combinations of catalase with superoxide dismutase have also been investigated.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Arg.*: Arlon Cronos; *Canad.*: UltraCare†; *Gr.*: Pulvo 47; Pulvo-Hexa; *Ital.*: Citrizan Antibiotico; *Mex.*: Avitil; *NZ*: Oxysept 1 Step; *Thai.*: Pulvo 47†; *Turk.*: Pulvo 47; *USA*: UltraCare.

Catechu

Gambier; Gambir; Pale Catechu; Гамбир.

CAS — 8001-48-7.

ATC Herb — HA07XA5013 (Uncaria gambir: extract); HA01WA5008 (Uncaria gambir: extract).

UNII — 3NJQ5D856N.

NOTE. Distinguish from Black Catechu (p. 2457.3).

Pharmacopoeias. In *Jpn*. Also in *BP(Vet)*.

BP(Vet) 2014: (Catechu). A dried aqueous extract of the leaves and young shoots of *Uncaria gambier* occurring as dull pale greyish-brown to dark reddish-brown cubes. Odourless or almost odourless.

Profile

Catechu is an astringent and has been given in preparations for the treatment of diarrhoea and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Diarcalm†; *Fr.*: Elixir Bonjean†; *Indon.*: Entrodiar†; *Ital.*: Flavion; Imoviral; *Rus.*: Travisil (Трависил); *S.Afr.*: Enterodyne†; SB Diarrhoea Mixture†; Tandpyndruppels†; *Thai.*: Patarver; *UK*: Chesty Cough Relief; Spanish Tummy Mixture.

CD4 Antibodies

Anti-CD4 Monoclonal Antibodies; Anticuerpos CD4; CD4mAb; Monoclonal CD4 Antibodies; Антитела Против CД4-Клеток.

Profile

Monoclonal antibodies raised against CD4 receptors are under investigation in the treatment of immunologically mediated disorders, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma, cutaneous T-cell lymphoma, psoriasis, and various other skin disorders, with the aim of decreasing and eliminating circulating helper T lymphocytes. They have also been tried in transplantation. CD4 antibodies investigated include: clenoliximab, keliximab, priliximab, and zanolimumab.

Cedar Wood Oil

Eastern Red Cedar Stem Oil; Oleum Cedri; *Juniperus virginiana* Oil; *Juniperus virginiana* Stem Oil; Red Cedar Oil; Red Cedar Stem Oil; Red Cedarwood Oil.

CAS — 8000-27-9.

UNII — PAD4FN7P2G.

NOTE. Distinguish cedar wood oil, obtained from species of *Juniperus virginiana*, and cedar leaf oil, obtained from *Thuja occidentalis* (see Thuja, p. 2629.3).

Profile

Cedar wood oil (cedarwood oil; red cedar oil) is obtained from red cedar, *Juniperus virginiana* (Cupressaceae). Cedar wood oil is used in perfumery and is included in preparations for nasal congestion and various skin disorders. It is also used in aromatherapy. Atlantic cedarwood oil (Atlas cedarwood oil) from *Cedrus atlantica* (Pinaceae) and oils from the wood of other species of *Juniperus* and *Cedrus* are used similarly.

Homoeopathy

Red cedar has been used in homoeopathic medicines under the following names: Juniperus virginiana; Juniperus virg.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Wick Vaporub; *Canad.*: Artriben†; *Fr.*: Activox; *Gr.*: EKS; Revigel; *Hung.*: Kinder Luuf Balsam; *India*: Healplus; *Mon.*: Dermagor Betacade; *NZ*: Vicks Vaporub; *Port.*: Betacade; *Swed.*: Vicks Vaporub; *UK*: No-Sor Vapour Rub.

Celery

Apio; Apium; Celery Fruit; Celery Seed; Сельдерей.

CAS — 8015-90-5 (celery oil).

ATC Herb — HA03WA5003 (Apium graveolens: fruit); HM01AW5002 (Apium graveolens: fruit); HA03WA5002 (Apium graveolens: essential oil); HG04BW5004 (Apium graveolens: fruit).
UNII — 15V0BLB71G (celery); XSZ4RMF8NF (celery juice); 1240X9B0BZ (celery root); 1G1EAA320L (celery seed); 44IDY6DTKX (celery stem/top).

Uses and Administration

Celery consists of the dried ripe fruits of *Apium graveolens* (Umbelliferae). Other parts of the plant are also used. Celery is reported to have diuretic properties and has been included in herbal preparations for rheumatic disorders. Celery oil has also been used similarly. Allergic and photoallergic reactions have been reported.

Celery also has culinary uses. Celery seed oil is used in aromatherapy.

Homoeopathy

Celery has been used in homoeopathic medicines under the following names: Apium graveolens; Apium. gr.

References.

1. Houghton P. Bearberry, dandelion and celery. *Pharm J* 1995; **255:** 272–3.

Insect repellent. A hexane extraction of celery seed has shown promise as a mosquito repellent.[1]

1. Tuetun B, *et al.* Repellent properties of celery, *Apium graveolens* L., compared with commercial repellents, against mosquitoes under laboratory and field conditions. *Trop Med Int Health* 2005; **10:** 1190–8.

Interactions

For a report of severe phototoxicity occurring in a patient who had consumed celery soup before undergoing PUVA therapy, see Interactions under Methoxsalen, p. 1714.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.:*** Calmtabs; ***Austral.:*** Arthri Plus†; Arthriforte†; Arthritic Pain Herbal Formula 1†; Arthro-Eze; Boswellia Complex; Celery 3000; Devils Claw Plus†; Masculine Herbal Complex; Olf†; ***Canad.:*** Herbal Diretic; Herbal Diuretic; ***Chile:*** Draineur; ***Fr.:*** Biofirm; ***India:*** Agloliv; Aptizooom; Flexi-muv†; Gasex; Himcospaz; Ojus; ***Indon.:*** Tensigard; ***Philipp.:*** Ruflex; ***Singapore:*** Ruflex; ***UK:*** Mixed Vegetable Tablets; Modern Herbals Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain; Vegetex; ***Ukr.:*** Nephrocare (Нефрокеа); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Tazalok (Тазалок).

Cellobiose

Glucobiosa; Целлобиоза.
4-O-β-D-Glucopyranosyl-D-glucose.
$C_{12}H_{22}O_{11}$=342.3
CAS — 528-50-7.

Profile

Cellobiose is an indigestible disaccharide that has been used to assess intestinal permeability. It has been used as an alternative to lactulose in the differential sugar absorption test (p. 1851.1).

Cellulase *(USAN)*

Celulasa; EC 3.2.1.4; Целлюлаза.
CAS — 9012-54-8.

Profile

Cellulase is a concentrate of cellulose-splitting (cellulolytic) enzymes derived from *Aspergillus niger* or other sources. It is used in food processing and has been given orally with other digestive enzymes for its supposed benefit in minor digestive disorders such as dyspepsia and flatulence. Hemicellulase has been given for similar purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.:*** Pancrelase; ***Rus.:*** Festal (Фестал).

Multi-ingredient Preparations. ***Arg.:*** Arnol; Biletan Enzimatico; Biluen Enzimatico; Dom-Pollenzim; Gastridin-E; Pakinase; Pankreon Total; Pollenzim; ***Austral.:*** Vegie Digestaid; ***Belg.:*** Digestomen; ***Braz.:*** Dasc†; Digecap-Zimatico; Essen; Sintozima†; ***Canad.:*** Digesdyn; Digesta; Multi-Zyme†; Synergy Defense; ***China:*** Dages (达吉); Mite (米特); ***India:*** Dipep; Enzovit; Festal; ***Indon.:*** Cotazym Forte; ***Mex.:*** Dixiflen; Espaven Enzimatico; Ochozim; Onoton; ***Philipp.:*** Spasmo-Canulase; ***Port.:*** Colerin-P†; Espasmo Canulase†; Fermetone Composto; ***Rus.:*** Biofestal (Биофестаь); Ipental (Ипентал)†; Pheresthal (Ферестал); ***S.Afr.:*** Spasmo-Canulase†; ***Switz.:*** Spasmo-Canulase; ***Turk.:*** Flaton; ***Ukr.:*** Festal (Фестал); ***USA:*** Digex†; Enzyme; Similase Jr; ***Venez.:*** Stamyl.

Centaury

Centaurea menor; Centaurée, petite; Centaurii Herba; Centaurii Minoris Herba; Ezerjófű; Feverwort; Hiel de la tierra; Petite Centaurée; Rohtorantasappi; Širdažolių žolė; Tausendgüldenkraut; Tusengyllenört; Zeměžlučová nať; Ziele centurii.
ATC Herb — HA09WA5004 (Centaurium erythraea: herb).
UNII — 57X4TSH58S (Centaurium erythraea); B204P54Z1F (Centaurium erythraea extract); ZL25KMM82T (Centaurium erythraea flowering top).

NOTE. The name Feverwort has also been used as a common name for *Eupatorium perfoliatum* (see Boneset, p. 2459.1).

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

Ph. Eur. 8: (Centaury). The whole or fragmented dried flowering aerial parts of *Centaurium erythraea*. It has a bitter taste. Protect from light.

Uses and Administration

Centaury is used as a bitter, including for appetite loss and dyspepsia.

Adverse Effects

Effects on the liver. A report[1] of hepatotoxicity possibly associated with the use of *Copaltra*, a herbal preparation marketed as an adjunct in the treatment of diabetes mellitus and containing centaury and *Coutarea latiflora* (copalchi) (p. 2487.3). A further 5 cases had been reported to the French pharmacovigilance network.

1. Wurtz A-S, *et al.* Possible hepatotoxicity from Copaltra, an herbal medicine. *Ann Pharmacother* 2002; **36:** 941–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria:*** China-Eisenwein†; Magentee St Severin; Mariazeller; Pervivo; ***Braz.:*** Camomila; ***Canad.:*** Floradix Tab†; Formula T4†; ***Cz.:*** Stomaran; ***Fr.:*** Diatisan†; Tisane D'Ars†; Tisane Hepatique de Hoerdt†; ***Ger.:*** Amara-Tropfen; Canephron N; Montana N; ***Hung.:*** Bittner; ***Pol.:*** Pervivo; ***Rus.:*** Canephron N (Канефрон Н); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); ***S.Afr.:*** Amara†; Clairo†; ***Switz.:*** Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Metabol; Tisane pour l'estomac; ***UK:*** Cystipret; ***Ukr.:*** Canephron N (Канефрон Н); Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Vitokan (Витокан).

Homoeopathic Preparations. ***Canad.:*** Amaratopfen†; ***Fr.:*** Diacure; ***Ger.:*** Gastrin-Do; Gastroplant; ***UK:*** Laxadoron.

Cereus

Cacto grandifloro; Cactus; Night-blooming Cereus; Pitahaya; Reina de la noche; Селеницереус Крупноцветковый (*Selenicereus grandiflorus*).

Profile

Cereus, the flowers and stems of night-blooming cereus (*Selenicereus grandiflorus*; *Cactus grandiflorus*) (Cactaceae), is thought to have cardiac stimulant actions and has been used in various cardiovascular disorders. It has also been used as an anthelmintic and in the treatment of rheumatism.

Homoeopathy

Cereus has been used in homoeopathic medicines under the following names: Cactus; Selenicereus grandiflorus; Cactus grandiflorus.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UAE:*** Mebo Scar.

Multi-ingredient Preparations. ***Switz.:*** Femisan.

Homoeopathic Preparations. ***Austria:*** Cactus compositum; Corasan; ***Canad.:*** Menopause L122; Soludor†; ***Chile:*** Ikoplex No 6; Lachess; ***Fr.:*** Abbe Chaupitre no 20†; Crataegus Complexe No 15; Lachesis Complexe No 122; Poconeol no 31; Poconeol no 5; Soludor; Strophantus Compose; Vinicard†; ***Ger.:*** A-Bomin; Angioton H; Angioton S†; Arte-cyl Ho-Len-Complex; Aurum-Gastreu S R2; Cardioselect N; Cefangipect H†; Cefangipect†; Cefavora Cor; Confludin N; Conva-cyl Ho-Len-Complex; Cor Plus; Cor; Corselect N; Corvipas SL; Crataegus comp; Crataegus Herzcomplex; Derivatio H; Derivatio; Diacard; HanoCor N; Homviotensin; Infi-Camphora; Lowe-Komplex Nr 10; Lycoaktin; Myonasan; Naranocor HM; Pectapas CPL; Pectapas SL; Pectapas; Schworocard; Steicardin N†; Strophanthus comp; Truw Gold; ***Neth.:*** Cralonin H; ***Switz.:*** Gouttes d'Or.

Ceruletide *(BAN, USAN, rINN)*

Caerulein; Cerulein; Ceruleína; Ceruletid; Ceruletida; Cérulétide; Ceruletidum; FI-6934; 883-S; Serulétidi; Церулетид.
$C_{58}H_{73}N_{13}O_{21}S_2$=1352.4
CAS — 17650-98-5 (ceruletide); 71247-25-1 (ceruletide diethylamine).
ATC — V04CC04.
ATC Vet — QV04CC04.
UNII — 888Y08971B.

NOTE. The name Ceruleinum has been applied to Indigo Carmine (p. 2532.2).

Description. Ceruletide is a decapeptide amide originally isolated from the skin of the Australian frog, *Hyla caerulea*, and other amphibians. Ceruletide may exist as a salt with 1 to 3 moles of diethylamine (ceruletide diethylamine).

Uses and Administration

Ceruletide is structurally related to pancreozymin (p. 2582.1) and has similar actions. When given parenterally it stimulates gallbladder contraction and relaxes the sphincter of Oddi; it also causes an increase in the secretion of pancreatic enzymes and stimulates intestinal muscle.

As ceruletide diethylamine it is used as an aid to diagnostic radiology and in the management of paralytic ileus. It has also been used in tests of pancreatic exocrine function (see under Pancreatitis, p. 2580.2), sometimes with secretin (p. 2612.2); these studies generally require duodenal intubation of the patient and examination of duodenal aspirate and are rarely performed.

For most radiographic procedures of the biliary and digestive tracts ceruletide diethylamine has been given by intramuscular injection in a dose equivalent to 300 nanograms/kg of ceruletide. Doses equivalent to 1 to 2 nanograms/kg per minute have been given by intravenous infusion in pancreatic function tests and in the treatment of paralytic ileus.

Adverse Effects

Ceruletide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Hypotensive reactions may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.:*** Takus†.

Cetyl Myristoleate

CMO; Hexadecyl Myristoleate; Palmityl Myristoleate; Цетил Миристолеат.
Hexadecyl (Z)-tetradec-9-enoate.
CAS — 64660-84-0.
UNII — 87P8K33Q5X.

Profile

Cetyl myristoleate is a cetyl ester (p. 2178.2) that has been suggested to be associated with resistance to arthritis in *mice*. Mixtures of cetyl esters containing mainly cetyl myristoleate have been given orally as nutritional supplements and have also been used topically in the management of osteoarthritis and musculoskeletal disorders.

References.

1. Diehl HW, May EL. Cetyl myristoleate isolated from Swiss albino mice: an apparent protective agent against adjuvant arthritis in rats. *J Pharm Sci* 1994; **83:** 296–9.
2. Hesslink R, *et al.* Cetylated fatty acids improve knee function in patients with osteoarthritis. *J Rheumatol* 2002; **29:** 1708–12.
3. Kraemer WJ, *et al.* Effect of a cetylated fatty acid topical cream on functional mobility and quality of life of patients with osteoarthritis. *J Rheumatol* 2004; **31:** 767–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India:*** Cartizole Plus; Celadrin; ***Indon.:*** Flexasur; Flexasur; ***Malaysia:*** Flexasur.

Cevimeline Hydrochloride *(USAN, rINNM)*

AF-102; AF-102B; Cevimelina, hidrocloruro de; Cévimeline, Chlorhydrate de; Cevimelini Hydrochloridum; FKS-508; Hidrocloruro de cevimelina; SND-5008; SNI-2011; SNK-508; Цевимелина Гидрохлорид.

(±)-cis-2-Methylspiro[1,3-oxathiolane-5,3′-quinuclidine] hydrochloride hemihydrate.
$C_{10}H_{17}NOS,HCl,\frac{1}{2}H_2O$=244.8
CAS — 107233-08-9 (cevimeline); 153504-70-2 (cevimeline hydrochloride).
ATC — N07AX03.
ATC Vet — QN07AX03.
UNII — P81Q6V85NP.

Uses and Administration

Cevimeline is a selective muscarinic M_1 agonist used to improve the symptoms of dry mouth (see p. 2175.3) in patients with Sjögren's syndrome. It is given orally as the hydrochloride in doses of 30 mg 3 times daily.

Reviews.
1. Weber J, Keating GM. Cevimeline. *Drugs* 2008; 68: 1691–8.

Dementia. Muscarinic M_1 agonists such as cevimeline have proved unsuccessful in relieving the symptoms of Alzheimer's disease (see p. 388.1).

Adverse Effects, Treatment, and Precautions

As for Neostigmine, p. 688.2 and p. 688.3.

Sweating is a common problem with cevimeline; patients who sweat excessively should be advised to drink extra fluids to avoid dehydration. Cevimeline should not be given when miosis is undesirable such as in patients with acute iritis or angle-closure glaucoma. Blurred vision may affect the performance of skilled tasks. In addition cevimeline should be given with care to those with renal calculi or with biliary-tract disorders. It should also be used with caution in patients deficient in the cytochrome P450 isoenzyme CYP2D6 who may be at a higher risk of adverse effects.

Interactions

As for Neostigmine, p. 688.3.

Drugs that inhibit cytochrome P450 isoenzymes CYP2D6, CYP3A3, or CYP3A4 inhibit the metabolism of cevimeline.

Pharmacokinetics

After oral doses cevimeline is absorbed from the gastrointestinal tract; peak concentrations are reached in 1.5 to 2 hours. The rate and extent of absorption are decreased when given with food. Cevimeline is less than 20% bound to plasma proteins. It is metabolised in the liver by cytochrome P450 isoenzymes CYP2D6, CYP3A3, and CYP3A4. Cevimeline is mainly excreted in the urine, mainly as metabolites; about 0.5% of a dose is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Evoxac.

Chamomile

Camomila; Camomille romaine, fleur de (chamomile flower, Roman); Chamomillae romanae flos (chamomile flower, Roman); Heřmánkový květ (matricaria flower); Kamillavirágzat (matricaria flower); Kamomillankukka (matricaria flower); Kamomillankukka, roomalainen (chamomile flower, Roman); Kamomillblomma (matricaria flower); Kamomillblomma, romersk (chamomile flower, Roman); Koszyczek rumianku (matricaria flower); Květ heřmánku římského (chamomile flower, Roman); Manzanilla; Matricaire, fleur de (matricaria flower); Matricariae flos (matricaria flower); Ramunėlių žiedai (matricaria flower); Római kamillavirág (chamomile flower, Roman); Tauriųjų didramunių žiedai (chamomile flower, Roman); Ромашка.
ATC Herb — HA09WA5006 (Chamaemelum nobile: flower); HA03WB5001 (Chamaemelum nobile: flower); HA03AW5010 (Chamaemelum nobile: flower); HN05CM5013 (Matricaria recutita: flower); HM01AW5014 (Matricaria recutita: flower); HA01WX5001 (Chamaemelum nobile: flower); HD03WX5011 (Matricaria recutita: flower); HG02WB5001 (Chamaemelum nobile: flower); HA03WB5002 (Matricaria recutita: flower); HA03AW5034 (Matricaria recutita: flower).
UNII — FGL36B5T2X (chamomile tea); G0R4UBI2ZZ (Matricaria recutita).

Description. The name Chamomile is used for the dried flowerheads from 2 species of *Compositae* having similar medicinal properties:

- Chamomile from *Anthemis nobilis* (*Chamaemelum nobile*) is known as Chamomile Flowers, Chamomillae Romanae Flos, Manzanilla Romana, or Roman Chamomile Flower.
- Chamomile from *Matricaria recutita* (*Chamomilla recutita*) is known as Camomile Allemande, Camomilla, Chamomilla, Chamomillae Anthodium, Flos Chamomillae, Flos Chamomillae Vulgaris, German Chamomile, Hungarian Chamomile, Kamillenblüten, Manzanilla Ordinaria, Matricaria Flower, or Matricariae Flos

Pharmacopoeias. *Eur.* (see p. vii) includes chamomile from *Anthemis nobilis* and *Matricaria recutita*. *US* includes chamomile from *Matricaria recutita*.

Eur. also includes Matricaria Oil.

Ph. Eur. 8: (Chamomile Flower, Roman; Chamomile Flowers BP 2014). The dried flowerheads obtained from the cultivated double variety of *Anthemis nobilis* (*Chamaemelum nobile*), containing not less than 0.7% v/w of essential oil, calculated with reference to the dried drug. It has a strong characteristic odour. Protect from light.

Ph. Eur. 8: (Matricaria Flower; Matricariae Flos; Matricaria Flowers BP 2014). The dried flowerheads obtained from *Matricaria recutita* (*Chamomilla recutita*), containing not less than 0.4% v/w of blue essential oil and 0.25% of apigenin-7-glucoside, calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Matricaria Oil; Matricariae Aetheroleum). The blue essential oil obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *Matricaria recutita* (*Chamomilla recutita*). There are 2 types of matricaria oil which are characterised as rich in bisabolol oxides, or rich in levomenol. Store in a well-filled, airtight container at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Chamomile). The dried flowerheads of *Matricaria recutita* (*Matricaria chamomilla, Matricaria chamomilla* var. *courrantiana, Chamomilla recutita*) (Asteraceae alt. Compositae). It contains not less than 0.4% of blue volatile oil, not less than 0.3% of apigenin-7-glucoside, and not less than 0.15% of bisabolane derivatives, calculated as levomenol. Protect from light.

Uses and Administration

Chamomile has been applied externally as a poultice in the early stages of inflammation, and preparations containing chamomile or extracts of chamomile (including the oil or a constituent, chamazulene), have been used for skin disorders, including the prevention and treatment of cracked nipples and nappy rash. Chamomile German oil and Chamomile Roman oil are used in aromatherapy. 'Chamomile tea' is a domestic remedy for indigestion and has also been reported to have hypnotic properties.

Homoeopathy

Chamomile has been used in homoeopathic medicines under the following names: Anthemis nobilis; Anthemis nob; Chamomilla; Cham.

Reviews.
1. Berry M. The chamomiles. *Pharm J* 1995; 254: 191–3.
2. WHO. Flos Chamomillae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/11.html (accessed 04/02/10)
3. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). *Phytother Res* 2006; 20: 519–30.
4. Gardiner P. Complementary, holistic, and integrative medicine: chamomile. *Pediatr Rev* 2007; 28: e16–e18.

Adverse Effects

Chamomile has been reported to produce contact sensitivity and anaphylaxis.

Hypersensitivity. References.
1. Van Ketel WG. Allergy to Matricaria chamomilla. *Contact Dermatitis* 1987; 16: 50–1.
2. McGeorge BC, Steele MC. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis* 1991; 24: 139–40.
3. Rodriguez-Serna M, *et al.* Allergic and systemic contact dermatitis from Matricaria chamomilla tea. *Contact Dermatitis* 1998; 39: 192–3.
4. Jensen-Jarolim E, *et al.* Fatal outcome of anaphylaxis to camomile-containing enema during labor: a case study. *J Allergy Clin Immunol* 1998; 102: 1041–2.
5. Giordano-Labadie F, *et al.* Allergic contact dermatitis from camomile used in phytotherapy. *Contact Dermatitis* 2000; 42: 247.
6. Foti C, *et al.* Contact urticaria from Matricaria chamomilla. *Contact Dermatitis* 2000; 42: 360–1.
7. de la Torre Morín F, *et al.* Clinical cross-reactivity between Artemisia vulgaris and Matricaria chamomilla (chamomile). *J Investig Allergol Clin Immunol* 2001; 11: 118–22.
8. Vandenplas O, *et al.* Occupational asthma caused by chamomile. *Allergy* 2008; 63: 1090–2.
9. Andres C, *et al.* Anaphylactic reaction to camomile tea. *Allergol Int* 2009; 58: 135–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Kamillosan; *Belg.*: Babygencal†; Kamillosan; *Braz.*: Ad-Muc; Kamillosan; *Canad.*: Paraterol†; *Cz.*: Hermankovy; Kamillosan†; *Fr.*: Camolid; *Ger.*: Kamillen-Bad Ritsert†; Kamillenbad Intradermi†; Kamillin; Kamilosan†; Matmille†; PC 30 N†; *Hong Kong*: Camoderm†; *India*: Kamillosan; Kamillosan; *Indon.*: Kamillosan; *Irl.*: Kamillosan; *Ital.*: Ceru Spray; Milla; *Mex.*: Balsamo Nordin; Kamillosan; *Pol.*: Azulan; Azuseptol; *Port.*: Kamilosan; *Rus.*: Romasulan (Ромазулан); *S.Afr.*: Ashton & Parsons Infants Powders†; Kamillosan†; *Switz.*: Kamillex; Kamillin Medipharm; Kamillofluid; Kamillosan; *Turk.*: Parodontax; *UK*: Ashton & Parsons Infants Powders; Kamillosan; *Venez.*: Kamillen Kamillosan.

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

Homoeopathic Preparations. *Austral.*: Allergy Relief; Calm; Childrens Sleep; Colic Relief; Earache Relief†; Sleep & Insomnia Relief; Teething Relief; *Austria*: Avena Med Complex; Birkenkohle comp; Daram; Echinacea-Cosmoplex; Erbiode Regelbeschwerden; Notta; Ohrentropfen Similasan; Osanit Chamomilla; Osanit Zahnungskugelchen; Otodolor; Otovowen; Traumeel; Valerianaheel; Zahnkugelchen; *Canad.*: Calms Forte 4 Kids; Calms Forte; Calsom†; Camilia; Col 138†; Colic; Den 141†; Diarrex; Diarrhea; Earache; Formula DM 210†; Hylands Formula C; Hylands Formula CF; Hylands Kinder-CL†; Hylands Kinder-T†; Indigestion†; Jet Lag; Kid's Colic; Kids' Teething; Lemon Balm†; Quietude; Spascupreel; Tee Complex†; Teething; Traumeel; Valerianaheel Comp†; Viburcol; *Chile*: Gug/X†; *Cz.*: Sedalia; Spascupreel S†; Traumeel; Viburcol; *Fr.*: Abbe Chaupitre no 18†; Abbe Chaupitre no 30†; Abbe Chaupitre no 43†; Abbe Chaupitre no 7; Abbe Chaupitre no 83†; Arthro-Drainol; Basilicum Complexe No 96; Camilia; Gelsemium Complexe No 70; Hedera Complexe No 120; Hypophysis Complexe No 31†; L 107; L 25; Poconeol no 37; Quietude; Ricinus Compose; *Ger.*: A-Bomin; Angi Truw N; Birkenkohle comp; Cefaspasmon N†; Cocculus Oligoplex; dysto-loges N; Entero-Gastreu S R4; Entzundungstropfen; Galloselect; Gastrin-Do; Gastro-Plantin N†; Infihepan; Jsostoma S; Magen-Darmtropfen N; Meno-cyl L Ho-Len-Complex; Osanit; Otovowen; Passiflora Complex†; Rapako comp; Regenaplex Haut W; Roth's Rotacard; Sedacalman; Spascupreel; Spasmosyx F; Stoma-Gastreu S R5; Traumeel S; Viburcol N; Weleda Fieber- und Zahnungszapfchen; Zahnungstropfen Escatitona; Zappelin N; *Hung.*: Spascupreel; Traumeel; Viburcol; *Neth.*: Artifleur; Auriculite; Collite; Entero-Gastreu R4; Gastrifleur; Homeocare Digesto; Homeocare keelspray; Kind 0-3 Chamodent; Kind 0-3 Cinababy; Kind 0-6 Kinditherm; Omnilite; Oteel H; Quietude†; Spascupreel H; Traumeel H; Traumeel S; Viburcol H; *Rus.*: Menalgin (Менальгин); Notta (Нотта); Traumeel S (Траумель С); *S.Afr.*: Chamomilla/Millefolium Comp†; Traumeel S; Viburcol; *Switz.*: Camilia; Quietude; Regenaplex Nr. 35b; Regenaplex Nr. 79; Traumeel; Viburcol N; *UK*: Teetha; *Ukr.*: Dentokind (Дентокинд); Enterocind (Энтерокинд); Kindinorm (Кинднинорм); Notta (Нотта); Traumeel S (Траумель С); *USA*: Preferred Remedies Sleep; Preferred Remedies Stress; Traumeel; *Venez.*: Traumeel.

Pharmacopoeial Preparations
Ph. Eur.: Matricaria Liquid Extract.

Chaparral

Gobernadora; Чапаррель.
UNII — PK0TXD049P (Larrea tridentata).

Uses and Administration

Chaparral is derived from the creosote bush, *Larrea tridentata* (Zygophyllaceae). It has been included in various herbal preparations but recommendations that products containing chaparral should not be consumed have been made in several countries because of serious toxicity—see below.

Masoprocol is an antineoplastic isolated from the creosote bush.

Effects on the liver. References.
1. Gordon DW, *et al.* Chaparral ingestion: the broadening spectrum of liver injury caused by herbal medications. *JAMA* 1995; 273: 489–90.
2. Batchelor WB, *et al.* Chaparral-induced hepatic injury. *Am J Gastroenterol* 1995; 90: 831–3.
3. Sheikh NM, *et al.* Chaparral-associated hepatotoxicity. *Arch Intern Med* 1997; 157: 913–19.
4. Kauma H, *et al.* Toxic acute hepatitis and hepatic fibrosis after consumption of chaparral tablets. *Scand J Gastroenterol* 2004; 39: 1168–71.

Adverse Effects

Ingestion of chaparral has been associated with severe hepatotoxicity including permanent liver failure.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Pollinosan†; *Switz.*: A Vogel Spray contre le rhume des foins; Pollinosan†.

Chebulic Myrobalan

Haritaki; He Zi; Ink Nut; Inknut; Jangi Harara; Myrobalan.
UNII — SH421PYG8O (Terminalia chebula); T6755WMN6R (Terminalia chebula bark); S8R4V700MK (Terminalia chebula fruit); 2UH8Y7160 (Terminalia chebula root).

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan — see Indian Gooseberry, p. 2532.2), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica* — see

Beleric Myrobalan, p. 2453.2; and *T. chebula*, Chebulic Myrobalan, above). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. In *Br.*

BP 2014: (Terminalia Chebula Fruit). The pericarp of mature fruits of *Terminalia chebula*. It contains not less than 20% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruit of chebulic myrobalan, *Terminalia chebula* (Combretaceae), is used in Ayurvedic medicine as a tonic and for a variety of disorders including both diarrhoea and constipation. The unripe fruit is also known as black myrobalan.

Other parts of the plant may also be used medicinally.

The traditional Ayurvedic medicine triphala is a combination of chebulic myrobalan, beleric myrobalan (p. 2453.2), and Indian gooseberry (p. 2532.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Triphala; *Hung.*: Herbadict; Livfit; Munipyrin; *India*: Abana; Ampucare; Bonnisan; Diabasic; Flexi-muv†; Geriforte; Geriforte; Herbolax; Intraliv; Jaundif; Koflet; Livasa; Liyurto; Megacure-DS; Menosan; Mentat; New-Livfit; Paedritone; *Malaysia*: Bonnisan; *Philipp.*: Cogent db+; *Rus.*: Fitovit (Фитовит); Pilex (Пайлекс); Travisil (Трависил); *Singapore*: Hemoglo; Imunomet; *Switz.*: Padma-Lax; Padmed Laxan; *UK*: Padma Circosan; *Ukr.*: Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†; Septilin (Септилин); Softovak (Софтовак); Travisil (Трависил); Trypsidan (Трипсидан)†.

Chenodeoxycholic Acid *(BAN, rINN)*

Acide Chénodésoxycholique; Ácido quenodeoxicólico; Acidum Chenodeoxycholicum; CDCA; Chenic Acid; Chenodeoksicholio rūgštis; Chenodesoxycholsäure; Chenodiol (USAN); Kenodeoksikolik Asit; Kenodeoksikoolihappo; Kenodeoxicholsyra; Kenodezoxikólsav; Kyselina chenodeoxycholová; Quenodeoxicólico, ácido; Хенодезоксихолевая Кислота.

3α,7α-Dihydroxy-5β-cholan-24-oic acid.

$C_{24}H_{40}O_4$=392.6

CAS — 474-25-9.

ATC — A05AA01.

ATC Vet — QA05AA01.

UNII — 0GEI24LG0J.

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

Ph. Eur. 8: (Chenodeoxycholic Acid). A white or almost white powder. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in dichloromethane.

Uses and Administration

Chenodeoxycholic acid is a naturally occurring bile acid (p. 2457.2). When given orally it reduces hepatic synthesis of cholesterol and provides additional bile salts to the pool available for solubilisation of cholesterol and lipids. It has been used for the dissolution of cholesterol-rich gallstones (p. 2639.1) in patients with a functioning gallbladder, in usual doses of about 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentrations seen overnight. Treatment may need to be given for up to 2 years, depending on the size of the stone. It should be continued for about 3 months after radiological disappearance of the stones. Chenodeoxycholic acid is also used in reduced doses with ursodeoxycholic acid (p. 2638.1).

Chenodeoxycholic acid has been used as a dietary supplement in neonates and children with inborn errors of bile acid synthesis: it has been used in the treatment of cerebrotendinous xanthomatosis; with cholesterol in the Smith-Lemli-Opitz syndrome; and with cholic acid for bile acid synthesis defects.

Cerebrotendinous xanthomatosis. Cerebrotendinous xanthomatosis is a rare autosomal recessive inborn error of bile acid metabolism. Accumulation of cholestanol in multiple organs and absence of chenodeoxycholic acid from bile results in a shift of bile acid metabolism to the cholestanol pathway. In a case report[1] of 4 family members with cerebrotendinous xanthomatosis followed up for 14 years after starting chenodeoxycholic acid therapy, 2 sisters who were started on treatment early at ages 2 and 7 years respectively, remained asymptomatic whereas only moderate improvement was seen in their 2 uncles who started treatment when already severely affected at ages 16 and 27 years respectively.

1. Berginer VM, *et al.* Chronic diarrhea and juvenile cataracts: think cerebrotendinous xanthomatosis and treat. *Pediatrics* 2009; 123: 143–7.

Adverse Effects and Precautions

As for Ursodeoxycholic Acid, p. 2639.2. Diarrhoea may occur more frequently than with ursodeoxycholic acid. A transient rise in liver-function test values and hypercholesterolaemia (low-density lipoprotein) have been reported with chenodeoxycholic acid.

Chenodeoxycholic acid is embryotoxic in some *animals*.

Interactions

As for Ursodeoxycholic Acid, p. 2639.3.

Pharmacokinetics

Chenodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes first-pass metabolism and enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile and, under the influence of intestinal bacteria, the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid. Some lithocholic acid is excreted directly in the faeces and the rest absorbed, mainly to be conjugated and sulfated by the liver before excretion in the faeces. Chenodeoxycholic acid also undergoes epimerisation to ursodeoxycholic acid.

References.

1. Crosignani A, *et al.* Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet* 1996; 30: 333–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Chenofalk†; Xenbilox; *Gr.*: Theramatic; *Indon.*: Chenofalk†; *Israel*: Chenofalk†; *Mex.*: Sulobil; *Neth.*: Chenofalk; *Port.*: Xebyl; *Rus.*: Chenofalk (Хенофальк); *Turk.*: Chenofalk; *USA*: Chenodal.

Multi-ingredient Preparations. *Ger.*: Lithofalk†; *Gr.*: Lithofalk; *Ital.*: Bilenor.

Cherry Laurel

Cherry Bay; English Laurel; Kirschlorbeer; Kirschlorbeerbaum; Laakerikirsikka; Lagerhägg; Laurier-Cerise; Laurier-amande; Lorbeerkirsche.

UNII — 516528LU0T (Prunus laurocerasus); *G3X35793OV* (Prunus laurocerasus *fruit oil*); *F26P2D4757* (Prunus laurocerasus *leaf*).

Pharmacopoeias. In *Fr.*

Profile

The leaves of cherry laurel, *Prunus laurocerasus* (*Cerasus laurocerasus*; *Laurocerasus officinalis*) (Rosaceae), are included in herbal medicines for cough. They contain the glycoside prulaurasin (laurocerasin; DL-mandelonitrile-D-glucoside) which decomposes to glucose, hydrocyanic acid (p. 2156.2), and benzaldehyde (p. 2171.1). They have been used in the preparation of Cherry-laurel Water and as the source of Oil of Cherry Laurel.

Cherry-laurel water was formerly used for nausea and vomiting, and as an eye lotion. The oil, with the hydrocyanic acid removed, has been used as a flavour.

Adverse effects are due to the content of hydrocyanic acid, and overdosage can be fatal.

Homoeopathy

Cherry laurel has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Cellutex; *Ital.*: Balsamina Kroner; *S.Afr.*: Spiritus Contra Tussim Drops†; *Spain*: Caltoson Balsamico†; Eupnol; *Switz.*: Sano Tuss.

Homoeopathic Preparations. *Fr.*: Boripharm No 31; *Ger.*: Cor Plus; Hypotonie-Gastreu R44; Pulmo-cyl Ho-Len-Complex; *UK*: Cough Drops.

Chicory

Achicoria de Bruselas; Achicoria de Café; Achicoria de Raíz; Belgium Endive; Blue Daisy; Blue Sailors; Chicoreé; Chicorée Amère; Chicorée de Bruxelles; Chicorée Sauvage; Chicória; Cikoria; Coffee Chicory; Coffee Weed; Common Chicory; Cykoria Podróżnik; French Endive; Hinduba; Kaffeezichorie; Radicchio; Radicheta; Salatzichorie; Succory; Wegwarte; Wild Chicory; Wilde Zichorie; Witloof; Wurzelzichorie.

UNII — 1KE45XD28S (chicory); HW54S00A89 (chicory flower); WBQ249COFR (chicory leaf); 090CTY533N (chicory root).

NOTE. The names Chicory and Endive are applied to several species of *Cichorium*.

Pharmacopoeias. In *Chin.*

Pol. includes the root.

Profile

The root and leaves of *Cichorium intybus* (Asteraceae) are included in herbal preparations for gastrointestinal disorders, biliary and hepatic disorders, and in tonics.

The roasted root has been used as a substitute for coffee and the leaves are eaten as a vegetable.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Draineur; *Fr.*: Biofirm; Detoxifiance; Obeflorine†; *Ger.*: Amara-Tropfen; *Hung.*: Diabess; Livfit; Majvedo es Detoxikalo; *Indon.*: Jesscool†; *Malaysia*: Bonnisan; *Pol.*: Liv 52; Urosan†; *Rus.*: Bonjigar (Бонджигар); Liv 52 (Лив 52); Liv 52 (Лив 52); *S.Afr.*: Amara†; *Singapore*: Liv 52; Liv 52; *Switz.*: Gouttes Amara; Kernosan 24; Liv 52; Metabol; *Ukr.*: Bonjigar (Бонджигар); Liv 52 (Лив 52).

Homoeopathic Preparations. *Canad.*: Amaratopfen†; *Fr.*: Poconeol no 67.

Chlorella

UNII — 5918V50NV8.

NOTE. *Chlorella vulgaris* and *Chlorella pyrenoidosa* are regarded as separate species by some sources.

Profile

The green alga *Chlorella vulgaris* (*C. pyrenoidosa*) (Oocystaceae) has been promoted as a nutritional supplement and as an adjunct to management of a range of diseases. Related species may be used similarly. The nutritional content varies with the method of preparation.

Chlorella is claimed to contain a substance known as Chlorella Growth Factor.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Growee; *Ital.*: Ginoday; *Philipp.*: Bomvital; Ceegeefer†; Celermin†; Cherifer; Chlorvytol†; Dreamvite; Dynavit; Enersel; EZ-Grow; Flexivit; Growee with Chlorella; Healthy Kidz; Kiddie Estamin; Kiddie Prime; Kiddirel; Lysadam Plus; Megavit; Multigen Plus; Multigrow; Nerveplex; Nutrazinc; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Optigrow; Pediafortan Forte-GE; Propan TLC; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita with Chlorella; Restor-F; Restor; Strevit; Supranutrol; Time-Cee; TLC Vita; Vigorvit; Vita SL Plus; Vitakids; *Singapore*: Growee†.

Chloroacetophenone

1-Chloroacetophenone; Cloroacetofenona; CN; CN Gas; Phenacyl Chloride; ω-Chloroacetophenone.

2-Chloroacetophenone.

C_8H_7ClO=154.6

CAS — 532-27-4.

UNII — 8885039IQG.

NOTE. The name mace is applied to solutions of chloroacetophenone.

Profile

Chloroacetophenone is a lachrymatory which is irritant to the skin and eyes. It has been used in a riot-control gas; it is described as a tear gas.

References.

1. Hu H, *et al.* Tear gas—harassing agent or toxic chemical weapon? *JAMA* 1989; 262: 660–3.
2. Treudler R, *et al.* Occupational contact dermatitis due to 2-chloracetophenone tear gas. *Br J Dermatol* 1999; 140: 531–4.
3. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; 22: 103–10.
4. Carron PN, Yersin B. Management of the effects of exposure to tear gas. *BMJ* 2009; 338: 1554–8.

8-Chlorotheophylline

Chlortheophylline.

8-Chloro-3,7-dihydro-1,3-dimethyl-1*H*-purin-2,6-dione.

$C_7H_7ClN_4O_2$=214.6

CAS — 85-18-7.

UNII — GE2UA340FM.

Profile

8-Chlorotheophylline is a xanthine derivative that forms stable compounds (teoclates) with various drugs. It is used in the manufacture of antihistamines such as promethazine teoclate (p. 638.2) and dimenhydrinate (p. 625.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Switz.*: Detensor.

Chondroitin Sulfate Sodium

Chondroitin 4-Sulfate (chondroitin sulfate A); Chondroitin Sulphate Sodium; Chondroïtine, sulfate sodique de; Chondroitini natrii sulfas; Chondroitinsulfat-Natrium; Chondroitin-sulfát sodná sůl; Chondroityny sodu siarczan; CSA (chondroitin sulfate A); Sodium Chondroitin Sulfate; Sodyum Kondroitin Sülfat; Хондроитин Сульфат Натрия.

$(C_{14}H_{19}NO_{14}SNa_2)_n$

CAS — 9007-28-7 (chondroitin sulfate); 9082-07-9 (chondroitin sulfate sodium); 24967-93-9 (chondroitin sulfate A); 39455-18-0 (chondroitin sulfate A sodium); 25322-46-7 (chondroitin sulfate C); 12678-07-8 (chondroitin sulfate C sodium).

ATC — M01AX25.

ATC Vet — QM01AX25.

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

Ph. Eur. 8: (Chondroitin Sulfate Sodium). A natural copolymer based mainly on the two disaccharides obtained from cartilage of both terrestrial and marine origins. Depending on the animal species of origin, it shows different proportions of 4-sulfate and 6-sulfate groups. A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Chondroitin Sulfate Sodium). The sodium salt of the sulfated linear glycosaminoglycan obtained from bovine, porcine, or avian cartilages of healthy and domestic animals used for food by humans. It consists mostly of the sodium salt of the sulfate ester of *N*-acetylchondrosamine (2-acetamido-2-deoxy-β-D-galactopyranose) and D-glucuronic acid copolymer. These hexoses are alternately linked β-1,4 and β-1,3 in the polymer. Chondrosamine moieties in the prevalent glycosaminoglycan are monosulfated mainly on position 4 and less so on position 6. Chondroitin sulfate sodium is extremely hygroscopic once dried. Store in airtight containers.

Uses and Administration

Chondroitin sulfate is an acid mucopolysaccharide that is a constituent of most cartilaginous tissues. It is used as the sodium salt, chondroitin sodium sulfate. It is given orally in reactive arthritides (see under Spondyloarthropathies, p. 14.3), such as gonococcal arthritis, and is often given with glucosamine (p. 2515.3) for its supposed chondroprotective action in musculoskeletal and joint disorders including osteoarthritis (see under Glucosamine, p. 2515.3). It is also used for its visco-elastic properties as an adjunct to ocular surgical procedures, including cataract extraction and intra-ocular lens implantation, and has been used for the relief of dry eye. A medium containing chondroitin sulfate A has been used to preserve corneas for transplantation. Chondroitin sulfate sodium has also been used as a means of replacing the glycosaminoglycan layer in the bladder in the treatment of interstitial cystitis (p. 2348.1). Chondroitin sulfate A and C are components of the heparinoid danaparoid (p. 1349.2).

Interactions

For reference to the effect of preparations containing chondroitin with glucosamine on warfarin, see under Dietary Supplements, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bioflogil; Dunason; Liquiprin; Lubrictin; Proft†; Structum; *Austria*: Condrosulf; *Belg.*: Lacrypos†; *Braz.*: Dunason; *Canad.*: Cell-fX; Uracyst; *Chile*: Condrosulf; *China*: An Pu Nuo Xin (安谱诺欣); Fu Zhi Ping (伏目平); Xin Qi Si (欣奇思); *Cz.*: Condral†; Condrosulf; Structum†; *Fin.*: Artosolv†; Cartexan; *Fr.*: Chondrosulf; Lacrypos†; Structum; *Ger.*: Gepan Instill; Sanaven; Uropol; *Hung.*: Condrosulf; *Indon.*: Viostin S; *Irl.*: Chondromel; *Ital.*: Condrosulf; *Malaysia*: Chondril†; Consulf; *Mex.*: Condrosulf; Dunason; Maxus; Structum; *Pol.*: Condral; Recalcin; Structum; *Port.*: Condrosulf†; Ossin; Structum; *Rus.*: Artra Chondroitin (Артра Хондроитин); Chondrogard (Хондрогард); Chondroitine-Akos (Хондроитин-Акос); Chondrolife (Хондролайф); Chondrolon (Хондролон); Chondroxide (Хондроксид); Mucosat (Мукосат); Structum (Структум); *Singapore*: Consulf†; *Spain*: Condrosan; Condrosulf; *Switz.*: Condrosulf; Structum; *Ukr.*: Arthron Chondrex (Артрон Хондрекс); Hondra-Syla (Хондра-Сила); Mucosat Neo (Мукосат Neo); Structum (Структум).

Multi-ingredient Preparations. *Arg.*: Adaxil Forte; Adaxil Plus; Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Cartiflex Forte; Ecosamina; Etinox; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucometil 3; Glucotrin Forte; Glucotrin VL; Lacrimax†; Maxus; Mecanyl Duo; Mecanyl K Duo; Optilac; Ostatac Duo; Reumosan Compuesto; Sigmaflex; Vartalon Duo K; Vartalon Duo; Viscoat†; *Austral.*: AB Ausbiobone; AB Carsa Giox; Bioflex†; Bonlutin; Duovisc; Formula for Joints; GenFlex 3†; GenFlex Plus†; Joint Formula Advanced with MSM Booster; Joint Formula Advanced; MeticGlucotin; OsteoRelief Plus MSM; OsteoEze Active + MSM; OsteoEze Active; PM Metic-Glucotin; Viscoat†; *Braz.*: Artrolive; Condroflex; *Canad.*: Uracyst Test Kit†; *Chile*: Artridol Duo; Dinaflex Duo; Eniflex Duo; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex†; *China*: Frecoseryl (润尔乐); Kang Ming (康明); *Fr.*: Arthrobiane; Capsaine; Chondrosteo; Dexsil Articulations; Dexsil Sport; Fleximax; Synotabs; Viscoat†; *Ger.*: DisCoVisc; Duovisc; Mobilat DuoAktiv; Viscoat; *Gr.*: Viscoat; *Hong Kong*: Arthritil Plus†; Doctor's Choice Fortified Joint Support†; *Hung.*: Porcerosito; *India*: Arth; Arthocare DS; Arthocare; Artifix; Bonit Join; Carticare; Cartifix; Cartigen Plus; Cartilamine DS; Cartilamine Forte; Cartisark; Cartivit; Cartiwel; Cartiz; Cartup; Conjoint; Flexi Cap; Flexibel; Freeflex; GC Flex; Gencart; Glutin; Intecar; Joint Guard; Jointace Forte; Jonty; Kondro; Mega Freeflex; Mobijoint; Necare; Orbone; Osteocip; Osteoflex; Ostiwel; Ostofit; Ostop; Ostovit; *Indon.*: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Artro; Bonic Plus; Bonic; Cartiflex; Cartin; Chondro-PA; Fitbon Plus; Flexor; Fripos; GCM; Joint Care Plus; Joint Care; Jointfit; Lavarix; Maxitrin†; Naturema; Nutrijoint; OA Forte; OA Plus; OA; Osamin; Ositin; Osmetin 3; Oste; Ostela; Osteoflam; Osteokom Forte; Osteokom; Osteokom; Osteonic; Osteor Plus; Osteor-C; Osteor; Osteotin; Ostine; Ostrimix; Osvion Plus; Rebone; Rheumatin Forte; Rheumatin; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Vostem; Vosteon; *Irl.*: Seven Seas Active Sport†; *Israel*: Mega Gluflex with MSN; Mega Gluflex; *Ital.*: Cartago; Cartijoint†; Condrorexil; DisCoVisc†; Fitogenase; Ginepausil; Joint Support; Reumil; Reumilase Plus; Reumilase SD; Viscoat; *Malaysia*: Conart; Cosamine Plus; Duovisc†; Viscoat†; *Mex.*: Actiman; Artiflex; Humylub Ofteno; Mex-Amina; Splash Tears; Vartalon Compositum; *Mon.*: Algicuivre; *NZ*: Viscoat; *Philipp.*: Artiflex; Cartifast-C; Flexxbon; Osteoaid; Viscoat; *Rus.*: Artra (Артра); Chondroitine-Akos (Хондроитин-Акос); Chondroxide (Хондроксид); Hondrofen (Хондрофен); KONDROnova (КОНДРОнова); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); *S.Afr.*: Duovisc†; Viscoat; *Singapore*: Artril C†; Artrilase; BCC; Duovisc; Glutilage Plus; Joint Care; JointFlex; Seven Seas JointCare; Viscoat†; *Spain*: Droglican; *Thai.*: Artrofort Complex; DisCoVisc; Duovisc; Viscoat; *Turk.*: Duovisc†; Jointace; Ultimate; Viscoat; *UK*: BackOsamine; Flexeze; GlucOsamax; Joint Action; Jointace; Jointace; Jointace; *Ukr.*: Arthron Complex (Артрон Комплекс); Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Chondrasil (Хондрасил)†; Chondroitin Complex (Хондроитин Комплекс); Chondroxide (Хондроксид); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; Hondra-Syla (Хондра-Сила); Movex Active (Мовекс Актив); Movex Comfort (Мовекс Комфорт); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); *USA*: Cosamin; DisCoVisc; Viscoat; *Venez.*: Artrosamin.

Pharmacopoeial Preparations

USP 36: Chondroitin Sulfate Sodium Tablets; Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Chrome Alum

Chromium Potassium Sulfate; Chromium Potassium Sulphate; Cromo, alumbre de; Хромовые Квасцы.

$KCr(SO_4)_2.12H_2O$=499.4

CAS — 10141-00-1 (anhydrous chrome alum); 7788-99-0 (chromium potassium sulfate dodecahydrate).

Profile

Chrome alum is used in leather tanning, as a mordant in dyeing, and for hardening gelatin in photographic materials. It has been used as a sclerosant in medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Scleremo.

Homoeopathic Preparations. *Ger.*: Pascallerg.

Chromium Trioxide

Anhidrido Crómico; Chromic Acid; Chromic Anhydride; Chromu(VI) tlenek; Cromo, trióxido de.

CrO_3=99.99

CAS — 1333-82-0.

UNII — 8LV49809UC.

Potassium Dichromate

Bichromate of Potash; Potassium Bichromate; Potasu dichromian.

$K_2Cr_2O_7$=294.2

CAS — 7778-50-9.

UNII — T4423518FM.

Pharmacopoeias. *Eur.* (see p. vii) includes for homoeopathic preparations.

Ph. Eur. 8: (Potassium Dichromate for Homoeopathic Preparations; Kalii Bichromas ad Praeparationes Homoeopathicas). Orange crystals. Freely soluble in water; practically insoluble in alcohol.

Profile

Chromium trioxide is a hexavalent chromium salt. Although chromium is an essential trace element (see p. 2055.3) hexavalent salts are mainly used in industry and are associated with acute and chronic toxicity; they are more dangerous than di- or trivalent compounds.

Hexavalent chromium salts are oxidising agents and solutions are corrosive. Repeated contact may cause eczematous dermatitis, particularly in hypersensitive persons and can also cause deep perforating ulcers known as 'chrome holes'. If inhaled, chromic dusts cause rhinitis and painless ulcers which may perforate the nasal septum; inhalation may cause severe lung damage and inflammation of the eyes. There may also be involvement of the CNS and there is an increased risk of lung cancer.

Acute poisoning after ingestion of hexavalent chromium salts may cause intense thirst, dizziness, abdominal pain with vomiting, and diarrhoea; hepatic injury, acute renal failure with anuria or oliguria, and peripheral vascular collapse may also result. Fatalities have occurred due to renal or hepatic damage.

Treatment of acute chromium poisoning is symptomatic and supportive. Protective measures should be taken when handling or working with chromium and its salts.

Chromium trioxide was formerly used as a caustic and astringent. Potassium dichromate has been used similarly.

Homoeopathy

Potassium dichromate has been used in homoeopathic medicines under the following names: kali bichromicum; kalium bichromicum; kaliumdichromat; kalii dichromas; kali-bi.

Adverse effects. The toxicity of chromium[1-4] is mainly associated with hexavalent chromium compounds and there have been reports of poisoning with ammonium dichromate,[5] chromium trioxide,[6] potassium dichromate,[7-9] and sodium dichromate.[10] Although treatment with ascorbic acid has been suggested there is little evidence of benefit and it is not generally recommended.[11]

1. WHO. Chromium. *Environmental Health Criteria 61.* Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/ehc/ehc/ehc61.htm (accessed 30/07/08)
2. Health and Safety Executive. The toxicity of chromium and inorganic chromium compounds. *Toxicity Review 21.* London: HMSO, 1989.
3. Barceloux DG. Chromium. *J Toxicol Clin Toxicol* 1999; 37: 173–94.
4. Dayan AD, Paine AJ. Mechanisms of chromium toxicity, carcinogenicity and allergenicity: review of the literature from 1985 to 2000. *Hum Exp Toxicol* 2001; 20: 439–51.
5. Meert KL, *et al.* Acute ammonium dichromate poisoning. *Ann Emerg Med* 1994; 24: 748–50.
6. Matey P, *et al.* Chromic acid burns: early aggressive excision is the best method to prevent systemic toxicity. *J Burn Care Rehabil* 2000; 21: 241–5.
7. Michie CA, *et al.* Poisoning with a traditional remedy containing potassium dichromate. *Hum Exp Toxicol* 1991; 10: 129–31.
8. Stift A, *et al.* Liver transplantation for potassium dichromate poisoning. *N Engl J Med* 1998; 338: 766–7.
9. Kolacinski Z, *et al.* Acute potassium dichromate poisoning: a toxicokinetic case study. *J Toxicol Clin Toxicol* 1999; 37: 785–91.
10. Ellis EN, *et al.* Effects of hemodialysis and dimercaprol in acute dichromate poisoning. *J Toxicol Clin Toxicol* 1982; 19: 249–58.
11. Bradberry SM, Vale JA. Therapeutic review: is ascorbic acid of value in chromium poisoning and chromium dermatitis? *J Toxicol Clin Toxicol* 1999; 37: 195–200.

Handling. Chromium trioxide is a powerful oxidising agent and is liable to explode in contact with small quantities of alcohol, ether, glycerol, and other organic substances.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Childrens Cough Relief; Childrens Runny Nose Relief; Earache Relief†; Respatona Chesty Cough & Nasal Congestion; Respatona Dry Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Snore Eze; Snorestop; *Austria*: Asinis; Globuli gegen Schnupfen Nr 3; Luffa Med Complex; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Tonsillopas; Tonsiotren; *Canad.*: Bioactiv H†; Bronchial Cough; Cat Complex†; Comp-Drops 5 Expectorant†; Coryzalia; Cough & Cold; Detox L37; Homeo-Form R†; Homeodel 21†; Homeovox;

Hylagene; Hylands Formula S; Hylands Sinus†; Hylaquell BC; Indigestion; Nareel†; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Snore Stop; *Chile*: Rinoplex; *Cz.*: Coryzalia; Homeovox; *Fr.*: Allium Cepa Compose; Coryzalia; Homeoaftyl; Homeodose 8†; Homeovox; Iodum Complexe No 118; Mercurius Cyanatus Complexe No 43†; Sinuspax; Thuya Complexe No 37; *Ger.*: Angina-Gastreu S R1; Gripps; Hevertotox; Hewallergia Complex; Muco-cyl L Ho-Len-Complex; Mucosa compositum; Odonton-Echtroplex; Rufebran gastro†; Schleimhaut-Komplex L Ho-Pu-Complex; Sinasal; Sinuselect N; Sinusitis Hevert SL; Sinusitis Hevert†; Sinusitis-Weliplex†; Tonsillopas; Tonsiotren H; *Hung.*: Coryzalia; Homeovox; Naso-Heel S; *Neth.*: Belachin-Gastreu R1; Coryzalia; Homeovox; Mucosa comp H; Snurdim; *Port.*: Coryzalia; Homeovox; *Rus.*: Asinis (Асинис); Cinnabsin (Цинна́бсин); Coryzalia (Корызалия); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); *Switz.*: A Vogel pour les sinus; Aceprin-N; Coryzalia; Homeovox; metasinusit; Nelsons Sinusit†; Sinusin; Sinuspax†; *Ukr.*: Asinis (Асинис); Cinnabsin (Цинна́бсин); Coryzalia (Корызалия); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); *USA*: Preferred Remedies Sinus.

Chromocarb Diethylamine *(rINN)*

Chromocarbe; Diéthylamine de; Chromocarbi Diethylaminum; Cromocarbo, dietilamina de; Dietilamina de cromocarbo; Хромокарба Диэтиламин.

The diethylamine salt of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid.

$C_{14}H_{17}O_4N$=263.3

CAS — 54940-39-0 (chromocarb).

UNII — R0O8TF63DH.

Profile

Chromocarb diethylamine is used to reduce capillary haemorrhage (including conjunctival haemorrhage) associated with various disorders, and for venous insufficiency. It is given orally in a dose of 200 mg 3 times daily. It is also used as eye drops; 1 or 2 drops of a 10% solution have been instilled up to 6 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Fludarene; *Port.*: Fradilen; *Spain*: Activadone.

Chrysoidine Hydrochloride Citrate

Crisoidina, hidrocloruro del citrato de; 4-Phenylazobenzene-1,3-diamine hydrochloride citrate; Azobenzene-2,4-diamine hydrochloride citrate.

$C_{12}H_{12}N_4.HCl.C_6H_8O_7$=440.8

CAS — 532-82-1 (chrysoidine hydrochloride); 5909-04-6 (chrysoidine hydrochloride citrate).

Profile

Chrysoidine hydrochloride citrate has been used as a dye but has been associated with tumours of the bladder.

Carcinogenicity. The development of tumours of the urinary bladder in anglers was possibly associated with the use of chrysoidine hydrochloride (chrysoidine Y; CI Basic Orange 2; Colour Index No. 11270) for colouring the maggots used as bait.[1-3]

1. Searle CE, Teale J. Chrysoidine-dyed bait: a possible carcinogenic hazard to anglers? *Lancet* 1982; i: 564.
2. Sole GM. Maggots dyed with chrysoidine: a possible risk to anglers. *BMJ* 1984; 289: 1043–4.
3. Massey JA, *et al.* Maggots dyed with chrysoidine. *BMJ* 1984; 289: 1451–2.

Chymopapain *(BAN, USAN, rINN)* ⊗

BAX-1526; Chymopapaine; Chymopapainum; EC 3.4.22.6; Kymopapaiini; Kymopapain; NSC-107079; Quimopapaina; Quimopapaina; Химопапаин.

CAS — 9001-09-6.

ATC — M09AB01.

ATC Vet — QM09AB01.

ATC Herb — HA09AA5002 (Carica papaya: extract).

UNII — 1UK146T40N.

Description. Chymopapain is a proteolytic enzyme isolated from the latex of papaya (*Carica papaya*), differing from papain in electrophoretic mobility, solubility, and substrate specificity. Molecular weight about 27 000.

Units

One nanokatal (nKat) is defined as the amount of chymopapain which produces 1 nanomole of *p*-nitroaniline per second from DL-benzoylarginine-*p*-nitroanilide substrate at pH 6.4 and 37 degrees.

In some countries CTE units have been used, defined as the amount of chymopapain that produces a hydrolysate from acid-denatured haemoglobin at pH 4.0 in one minute with an optical density at 275 nm equivalent to that of a tyrosine solution 0.0001%.

Uses and Administration

Chymopapain is used as an injection into the intervertebral disc in the treatment of sciatic pain and other symptoms secondary to herniation of intervertebral discs of the lumbar spine (chemonucleolysis).

Chymopapain injection should preferably be given under local, rather than general, anaesthesia. The dose for a single intervertebral disc is 2 to 4 nanokatals, with a maximum dose per patient of 8 nanokatals.

Chemonucleolysis. Dissolution of the disc by injection of chymopapain or other enzymes (chemonucleolysis) has been used as an effective alternative to surgery in patients with lumbar disc herniation (see Low Back Pain, p. 9.2). However, concerns about its safety have led to a decline in its use, and discectomy is often preferred.

References.

1. Nordby EJ, *et al.* Chemonucleolysis. *Spine* 1996; 21: 1102–5.
2. Brown MD. Update on chemonucleolysis. *Spine* 1996; 21 (24 suppl): 62S–68S.
3. Poynton AR, *et al.* Chymopapain chemonucleolysis: a review of 105 cases. *J R Coll Surg Edinb* 1998; 43: 407–9.
4. Wittenberg RH, *et al.* Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; 26: 1835–41.

Adverse Effects

The most important adverse effect of chymopapain is anaphylaxis, which can occur in up to about 1% of patients. It has resulted in fatalities and restricts use to a single treatment session per patient. Typical symptoms include angioedema, hypotension, laryngeal oedema and bronchospasm, shock, and cardiac arrest. Allergic skin reactions may also occur. Other reported reactions include headache, nausea and vomiting, paralytic ileus, urinary retention, thrombophlebitis, paraesthesias, foot-drop, and discitis. Severe muscle spasm and an increase in back pain are common. Paraplegia, acute transverse myelitis, and intracerebral and subarachnoid haemorrhage have occurred.

Incidence of adverse effects. A 1984 postmarketing surveillance study on a US chymopapain preparation for intradiscal injection (*Chymodiactin*) involved data from 29 075 patients (representing about 50% of the total number of vials sold).[1] Anaphylactic reactions were confirmed in 194 patients (0.67%), 2 of whom died. The incidence was higher in women than in men. In 52 cases the reaction occurred after the test dose. Serious neurological reactions reported were: cerebral haemorrhage (6 cases, 3 fatal; autopsy revealed that they had underlying cerebrovascular abnormalities); paraplegia (11 cases, 5 of which may have been due to incorrect needle placement); transverse myelitis with paraplegia (2 cases, after 2 and 3 weeks, with subsequent recovery); and seizures (2 cases on injection and 1 several days after the procedure). Twenty-two patients had discitis with severe back pain and spasm. In 9 cases bacteria could be cultured, and 1 patient subsequently developed fatal *Staphylococcus aureus* meningitis.

Another review[2] of serious reactions associated with chymopapain between 1982 and 1991 (including data from the earlier postmarketing study) involved 121 reports among about 135 000 patients. They included fatal anaphylaxis (7 cases), infections (24 cases), haemorrhage (32 cases), and neurological reactions (32 cases).

Both reviews concluded that careful attention to proper patient selection and correct techniques of intradiscal needle placement are the most important factors in avoiding adverse effects with chymopapain.

1. Agre K, *et al.* Chymodiactin postmarketing surveillance: demographic and adverse experience data in 29075 patients. *Spine* 1984; 9: 479–85.
2. Nordby EJ, *et al.* Safety of chemonucleolysis: adverse effects reported in the United States, 1982–1991. *Clin Orthop* 1993; 293: 122–34.

Precautions

Chymopapain should not be used in those patients with a known sensitivity to papaya proteins or in patients with progressive paralysis, or tumours of the spinal cord, or lesions of the cauda equina. Severe spondylolisthesis is also a contra-indication. It should not be given to patients with heart failure, coronary artery disease, or respiratory failure who may be at increased risk if anaphylaxis occurs, nor to patients receiving beta blockers.

Care is required in administering chymopapain to ensure that the injection is into the disc and not intrathecal. However, discography is not recommended since the use of contrast media may exacerbate neurotoxicity and may inactivate the enzyme.

The risk of allergic reactions associated with chymopapain is so high that no patient should ever receive it more than once. Tests to identify those most at risk and pretreatment with antihistamines (H_1 and H_2) and corticosteroids may be used, but facilities for the emergency management of anaphylactic reactions should always be to hand when giving patients chymopapain. The risk of anaphylaxis is higher in women.

Injection of more than one disc is associated with an increased frequency of neurological reactions; therefore, such injection should only be carried out after confirmation of definite further disc involvement.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Chymodiactin†.

Chymotrypsin *(BAN, rINN)* ⊗

Chimotripsinas; α-Chymotrypsin; Chymotrypsine; Chymotrypsinum; EC 3.4.21.1; Kimotripszin; Kymotrypsiini; Kymotrypsin; Quimotripsina; Химотрипсин.

CAS — 9004-07-3.

ATC — B06AA04; S01KX01.

ATC Vet — QB06AA04; QS01KX01.

UNII — BVS505O332.

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

Ph. Eur. 8: (Chymotrypsin). A proteolytic enzyme obtained by the activation of chymotrypsinogen extracted from the pancreas of beef. It contains not less than 5 microkatals in each mg. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 5.0. Solutions have a maximum stability at pH 3 and a maximum activity at about pH 8. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Chymotrypsin). A proteolytic enzyme crystallised from an extract of the pancreas gland of the ox, *Bos taurus* (Bovidae). It contains not less than 1000 USP units in each mg, calculated on the dried basis. A white to yellowish-white, crystalline or amorphous, odourless powder. An amount equivalent to 100 000 USP units is soluble in 10 mL of water and in 10 mL of sodium chloride 0.9%. Store in airtight containers at a temperature not exceeding 40 degrees.

Units

Various methods have been used to assay the potency of chymotrypsin. Ph. Eur. 8 expresses activity in terms of microkatals while USP 36 expresses in terms of USP units. Other units that may be encountered are FIP units, Armour units, and Denver (or Wallace or Wampole) units.

Uses and Administration

Chymotrypsin is a proteolytic enzyme that has been used in ophthalmology for the dissection of the zonule of the lens, thus facilitating intracapsular cataract extraction and reducing trauma to the eye. For this purpose a solution of chymotrypsin in a sterile diluent such as sodium chloride 0.9% has been injected to irrigate the posterior chamber.

Chymotrypsin has also been given, usually orally or topically, for its supposed action in reducing soft-tissue inflammation and oedema associated with surgery or traumatic injuries, and in patients suffering from upper respiratory-tract disorders.

Hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Wobenzym; *Braz.*: Parenzyme Analgesico; Parenzyme†; Thiomucase; *Canad.*: Wobenzym; *Cz.*: Wobenzym; *Gr.*: Chymoral; Itastab; Tricuval; *India*: Alfapsin D; Alfapsin; Ceze; Chymase; Chymin; Chymobel Plus; Chymobel; Chymoral; Chymosoz-D; Chymotas; Chymotrip; Chymutrip; Ficlo-Forte; Flamotryp; K-Trip Plus; K-Trip; Kymovil Plus; Omotrip; Optase-DC; Orthal Forte; Orthotime; Soluzyme; *Mex.*: Ochozim; Quimotrip†; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; *Port.*: Chimar; *Rus.*: Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); *Spain*: Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Quimodril; *Ukr.*: Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); *USA*: Bio-Zyme; *Venez.*: Wobenzym N.

Pharmacopoeial Preparations

USP 36: Chymotrypsin for Ophthalmic Solution.

Ciliary Neurotrophic Factor

CNTF; Factor neurotrófico ciliar; Цилиарный Нейротрофический Фактор.

NOTE. The name Axokine has been used as a trade mark for a neurotrophic factor related to ciliary neurotrophic factor. The name Axokine has also been used for a proprietary preparation of hydroxychloroquine sulfate (p. 655.2).

Profile

Ciliary neurotrophic factor (CNTF) is a nerve growth factor produced in neural tissues and released in response to injury. Recombinant CNTF has been investigated in motor neurone disease (p. 2605.2), peripheral neuropathy, and obesity. CNTF is also under investigation for the treatment of retinitis pigmentosa and atrophic (dry) age-related macular degeneration as an intra-ocular polymer implant containing human retinal epithelial cells that have been genetically modified to secrete CNTF.

References.

1. Miller RG, *et al.* A placebo-controlled trial of recombinant human ciliary neurotrophic (rhCNTF) factor in amyotrophic lateral sclerosis. *Ann Neurol* 1996; 39: 256–60.
2. Ettinger MP, *et al.* Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA* 2003; 289: 1826–32.
3. Sieving PA, *et al.* Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proc Natl Acad Sci U S A* 2006; 103: 3896–901.

Cimicifuga

Actée à grappes; Black Cohosh; Black Snakeroot; Bugbane; Cimicifuga; Cimicifugae rhizoma; Cohosh negro; Herbe aux Punaises; Цимицифуга.

ATC — G02CX04.

ATC Vet — QG02CX04.

ATC Herb — HG03WA5001 (Cimicifuga racemosa: rhizome); HM01AW5006 (Cimicifuga racemosa: rhizome).

UNII — K73E24S6X9 (Cimicifuga racemosa root); 1D114JZ36B (Cimicifuga dahurica root).

NOTE. Distinguish from Blue Cohosh, p. 2458.2.

Pharmacopoeias. *Chin.* includes the rhizome of *Cimicifuga heracleifolia, C. dahurica,* and *C. foetida.*

Eur. (see p. vii) and *US* include the rhizome and roots of *C. racemosa. US* also includes the powdered form.

Jpn includes the rhizome of *C. simplex, C. heracleifolia, C. dahurica,* and *C. foetida.*

Ph. Eur. 8: (Black Cohosh; Cimicifugae Rhizoma). The dried, whole or fragmented rhizome and root of *Cimicifuga racemosa* (*Actaea racemosa*). It contains not less than 1.0% of triterpene glycosides, expressed as monoammonium glycyrrhizate ($C_{42}H_{65}NO_{16}$ = 840.0) calculated with reference to the dried drug.

USP 36: (Black Cohosh). The dried rhizome and roots of *Actaea racemosa* (*Cimicifuga racemosa*). It contains not less than 0.4% triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$ = 660.8) with reference to the dried drug. Protect from light and moisture.

Uses and Administration

Cimicifuga, the roots of *Cimicifuga racemosa* (*Actaea racemosa*) (Ranunculaceae), is used for menopausal and gynaecological disorders and is included in preparations for coughs.

Homoeopathy

Cimicifuga has been used in homoeopathic medicines under the following names: Actaea racemosa; Actaea rac.; Cimicifuga racemosa; Cim. rac.

General references.

1. WHO. Rhizoma Cimicifugae Racemosae. *WHO Monographs on Selected Medicinal Plants,* volume 2. WHO: Geneva; 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/8.html (accessed 04/02/10)

Menopausal disorders. Cimicifuga is used in menopausal disorders, particularly for the relief of hot flushes but opinion varies as to its efficacy. While some systematic reviews[1,2] consider that its use is not supported by conclusive evidence others suggest that overall it might be of some benefit.[3]

1. Borrelli F, Ernst E. Black cohosh (*Cimicifuga racemosa*) for menopausal symptoms: a systematic review of its efficacy. *Pharmacol Res* 2008; 58: 8–14.
2. Palacio C, *et al.* Black cohosh for the management of menopausal symptoms: a systematic review of clinical trials. *Drugs Aging* 2009; 26: 23–36.
3. Shams T, *et al.* Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis. *Altern Ther Health Med* 2010; 16: 36–44.

Adverse Effects

A systematic review of the limited data available on adverse effects for cimicifuga concluded that adverse effects are generally mild and transient.[1] It has been reported that cimicifuga may cause dizziness, vertigo, headache, vomiting, and gastrointestinal irritation when taken in large doses.[2] From January 1998 to February 2005, Health Canada[3] had received 7 reports of adverse effects suspected of being associated with black cohosh, including dizziness, rash, pruritus, oedema, increased pulse, bradycardia, atrial fibrillation, changes in plasma-thyroid hormone concentration, vaginal bleeding, and convulsions. However, lack of data meant that causality could not be proved.

As of March 2006, the UK MHRA[2] had received 21 reports of **hepatotoxicity** associated with cimicifuga ingestion since 1998, which represented more than two-thirds of the total number of reports for any reaction related to cimicifuga. Likewise, there have been similar reports of hepatotoxicity in other countries including the USA, Germany, and Sweden.[2] Up to April 2006, 11 cases of liver impairment associated with cimicifuga had also been reported in Australia.[4] Adverse liver reactions reported worldwide have included abnormal liver function tests, jaundice, hepatitis, and liver failure.[2] In general, patients showed signs of recovery on stopping ingestion.[2] Some regulatory authorities consider that the available evidence supports a rare association between cimicifuga and risk of liver toxicity, even though the level of risk is difficult to determine.[2,5,6] They have recommended that warnings regarding potential adverse liver reactions should be added to product information and consumers are advised to stop taking cimicifuga if they develop symptoms of liver damage;[2,5-7] also, patients who have previously had liver or other serious health problems should consult their doctor before starting to take cimicifuga.[2,6]

1. Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003; 10: 58–64.
2. MHRA. UK Public Assessment Report. Black Cohosh (issued 31st July 2006). Available at: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalmedicines/CON2024279 (accessed 16/08/10)
3. Health Canada. Black cohosh: international reports of liver toxicity. *Can Adverse React News* 2005; 15 (3): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3_e.pdf (accessed 31/10/05)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Hepatotoxicity with black cohosh. *Aust Adverse Drug React Bull* 2006; 25: 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0604.pdf (accessed 25/05/06)
5. EMEA. EMEA Public statement on herbal medicinal products containing cimicifuga racemosae rhizoma (black cohosh, root) — serious hepatic reactions (issued 18th July 2006). Available at: http://www.emea.europa.eu/pdfs/human/hmpc/26925906en.pdf (accessed 01/11/07)
6. Australian Government Department of Health and Ageing: Therapeutic Goods Administration. Black cohosh (*Cimicifuga racemosa*): new labelling requirements and consumer information for medicines containing black cohosh (issued 29th May 2007). Available at: http://www.tga.gov.au/cm/0705blkcohosh.htm (accessed 01/11/07)
7. Health Canada. Health Canada is advising consumers about a possible link between black cohosh and liver damage (issued 18th August 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2006/2006_72_e.html (accessed 05/11/07)

Interactions

For a suggestion of a potential interaction between cimicifuga and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Pharmacokinetics

In a study[1] to investigate the pharmacokinetics of 23-epi-26-deoxyactein, one of the most abundant triterpene glycosides of black cohosh, the maximum concentration and area under the curve increased proportionately with dosage, and the half-life was about 2 hours. Less than 0.01% of 23-epi-26-deoxyactein was recovered in the urine after 24 hours. No acute toxicity or oestrogenic hormone effects were seen after single oral doses of a 75% ethanol extract of black cohosh containing 1.4, 2.8, or 5.6 mg of 23-epi-26-deoxyactein given to 15 healthy, menopausal women.

1. van Breemen RB, *et al.* Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh. *Clin Pharmacol Ther* 2010; 87: 219–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Menofem; *Austral.*: Pemular; *Austria*: Agnukliman; Jinda†; Klimadynon; Remifemin; Sanvita Meno; *Braz.*: Amenopam†; Aplause; Clifemin; Mencirax; Menocalm; Menocimed†; Tensiane†; *Canad.*: Women's Formula; *Chile*: Ginemaxim; *China*: Remifemin (莉芙敏); *Cz.*: Cesracimi; Cimisan†; Menofem; *Denm.*: Remifemin; *Fr.*: Cimipax†; *Ger.*: Cefakliman mono†; Cimisan†; Femi; Femikliman uno†; Femilla†; Feminon C; Galafem; Jinda; Klimadynon; Kofemin; Natu-fem; Remifemin; Sinelt†; *Hong Kong*: Klimadynon; *Hung.*: Cefakliman mono; Cimicin; Femitan†; Klimapur†; Remifemin; *Indon.*: Klimadynon†; Remifemin†; *Malaysia*: Cefakliman; Remifemin; *Mex.*: Avala; Clifenal†; Mensifem; *Norw.*: Remifemin; *Philipp.*: Remifemin; *Pol.*: Klimasol†; Menofem; Remifemin; *Rus.*: Klimadynon (Климадинон); *Singapore*: Klimadynon; Nopause; Remifemin; *Spain*: Aquimicix†; Avala†; Klimadynon; Remifemin; *Swed.*: Remifemin; *Switz.*: Cimifemine; Climavita; Femicine; Feminelle; Klimadynon; Maxifem†; Sanafem; *Thai.*: Femosa; Remifemin; *Turk.*: Klimadynon; *UK*: DiaBlack; DiaCimi; Femiplant; MenoCool; Menoherb; Menopret; Rumatix; *Ukr.*: Klimadynon (Климадинон).

Multi-ingredient Preparations. *Austral.*: Bone Complex; Cimicifuga Compound; Dong Quai Complex†; Dyzco†; Extralife Meno-Care†; Extralife PMS-Care†; Femi-Nan; Meno Support Plus; PM Meno-Care; Wild Yam Complex; *Austria*: Remifemin plus; *Canad.*: Calm-Aid†; Natural HRT Nightime; Natural HRT Phytoestrin; *Cz.*: Dr Theiss Schwedenbitter†; *Ger.*: Cimicifuga comp; Remifemin plus; *Hong Kong*: Phytoestrin†; *Hung.*: Remifemin Plus; *India*: Evepearl-MP; *Indon.*: Anstrep; Femosa Menose; Menoxa†; Osteopor; Pectum; Voldilex; *Ital.*: Biomineral Donna†; Hiperogyn; Pausanil; *Jpn*: Otsujito; Rikkosan; Shi-n'iseihaito; *Malaysia*: Gyno-Plus; *Pol.*: Klimax; Naturapia Menopauza; *Singapore*: Phytoestrin†; *UK*: DiaMenoCalm; Flash Fighters; Gerard House Reumalex; Menomood; Modern Herbals Rheumatic Pain; St Johnswort Compound; Vegetable Cough Remover; Vegetex; *Ukr.*: Lifemin (Лайфемин); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; *USA*: Estrocare.

Homoeopathic Preparations. *Austral.*: Pain & Fever Relief; *Austria*: Klimaktoplant; Mefem; Orgafem; Pascofemin; Remens; *Canad.*: Arthritis Pain Formula; Comp-Drops 9†; Headache & Migraine L77; Homeo-Form PMT†; Hylagesic APF; Hylands Formula MC; Hylands Menstrual Cramps†; Men Complex†; PMS; *Cz.*: Gelsemium-Homaccord; *Fr.*: Actheane; Cimicifuga Complexe No 21†; Helonias Compose; L 25; Phapax; *Ger.*: Agnus castus comp†; Agnus femin; Bomaklim; Calmvalera; Cefakliman N†; Cefakliman S; Cefakliman†; Cimicifuga N Oligoplex; DolorA; Dysmenorrhoe-Gastreu S R75; Elana†; Feminon N; Gelenk Albin; HanoFemin; Infi-Symphytum; Klimaktoplant N; Klimax-Gastreu S R10; Migrane-Gastreu R16; Naranofem†; Nervoid N; Neuro-Ginsan N; Ovarell; Pascofemin; Pascolibrin; Rheuma-Pasc; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Hung.*: Cimicifuga-Homaccord; Gelsemium-Homaccord; *Neth.*: Homeocare Cyclo; Klimaktolan; Klimax-Gastreu R10; Kruidvat Homeopathie Meno†; Mulimen H; *Rus.*: Climaxan (Климаксан); Diet-Comfort (Диет-Комфорт); Klimaktoplan (Климактоплан); Mirticam (Миртикам); Remens (Ременс); Uspokoi (Успокой); *Switz.*: Menosan†; Menstruasan; Regenaplex Nr. 21c; *Ukr.*: Capadol (Кападол); Homvio-Reuman (Хомвио-Ревман); Klimaktoplan N (Климактоплан Н); Remens (Ременс); *USA*: Estrex.

Pharmacopoeial Preparations

USP 36: Black Cohosh Fluidextract; Black Cohosh Tablets; Powdered Black Cohosh Extract.

Cinametic Acid *(rINN)*

Acide Cinamétique; Ácido cinamético; Acidum Cinameticum; Cinamético, ácido; Цинаметовая Кислота.

4-(2-Hydroxyethoxy)-3-methoxycinnamic acid.

$C_{12}H_{14}O_5$=238.2

CAS — 35703-32-3.

UNII — 3E3106052Y.

Profile

Cinametic acid has been used as a choleretic.

Cinchona Bark

Chinae Cortex; Chinarinde; Chininmedžių žievė; Chinovníková kůra; Cinchona; Cinchonae Cortex; Cinchonae Succirubrae Cortex; Jesuit's Bark; Kinankuori; Kinabark; Peruvian Bark; Quina; Quina Vermelha; Quiro, corteza del; Quinquina; Quinquina Rouge; Red Cinchona Bark; Vörös kinafa-kéreg; Хинная Кора.

ATC Herb — HA09WA5007 (Cinchona pubescens: bark); HN02BW5003 (Cinchona pubescens: bark); HP01BC5001 (Cinchona pubescens: bark).

UNII — 292E43P4I9 (cinchona bark); 03DF2I0XP1 (Cinchona pubescens); S96N10R972 (Cinchona pubescens bark); 056KT7S4VM (Cinchona calisaya); 77H72B7O3D (Cinchona calisaya bark).

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

Ph. Eur. 8: (Cinchona Bark). The whole or cut, dried bark of *Cinchona pubescens* (*Cinchona succirubra*), of *C. calisaya*, of *C. ledgeriana*, or of its varieties or hybrids. It contains a minimum of 6.5% of total alkaloids, of which 30 to 60% are quinine-type alkaloids. It has an intensely bitter, somewhat astringent taste. Protect from light.

Profile

Cinchona contains several alkaloids, including two pairs of optical isomers: quinine (p. 665.1) and quinidine, (p. 1481.1) and cinchonine and cinchonidine. Cinchona alkaloids have long been used for their antimalarial activity either singly, as quinine or quinidine, or in mixtures, such as totaquine. Quinidine is also used for its antiarrhythmic properties.

Cinchona bark is used as a bitter and is also employed in herbal remedies.

Homoeopathy

Cinchona bark has been used in homoeopathic medicines under the following names: Cinchonae cortex; China; China pubescens; China rubra; Cinchora succirubra; China officinalis; Cinchona; Cinchona officinalis; Cinc. of.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Albion; Bifena; *Austria*: Brady's-Magentropfen; China-Eisenwein†; Mariazeller; *Braz.*: Agua Inglesa†; *Fr.*: Quinimax; Quintonine†; *Ger.*: Amara-Pascoe; *Ital.*: Bulboshap†; Lozione Same Urto; *Pol.*: Melisana Klosterfrau; *S.Afr.*: Borstol Cough Remedy†; Versterkdruppels; *Switz.*: Enuton†.

Homoeopathic Preparations. *Austral.*: Vitatona Energy†; *Austria*: Acidum phosphoricum Med Complex; China Med Complex; Colchicum Med Complex; Gripagil-Grippetropfen mit Echinacea; Pertudoron†; Schnarchex; toxi-loges; *Canad.*: Aches & Pains; Bioactiv E†; Calms Forte 4 Kids; Carduus Plex†; Diarrhea; Formula ES 211; Formula FV 213; Formula Homeo QR 209†; Hepar Compositum; Hylagene; Hylands LCQ; Indigestion; Infilex†; L52 Cough & Cold; Leg Cramps with Quinine; Ton 2 Complex†; Vegetal Tonic; *Chile*: Bioactiv A; Bioactiv E; Bioactiv L; *Cz.*: Hepeel; Lehnigrip†; *Fr.*: Abbe Chaupitre no 18†; Abbe Chaupitre no 82†; Abbe Chaupitre no 88†; Adenocynesine†; Amanita Complexe No 75; Arnica Complexe no 1; Basilicum Complexe No 96; Boripharm No 15†; Boripharm No 1†; Chelidonium Compose; Cina Compose; Diaralia; Gastro-Drainol†; Grindelia Complexe No 58; Hepatocynesine†; Homeogene 22†; Hydrastis Compose; Hypophysis Complexe No 31†; L 107; L 25; L 28; L 52; Ledum Complexe No 81; Millefolium Complexe No 7†; Momordica Complexe No 109†; Nux Vomica Complexe No 49; Pertudoron; Tonique Vegetal; *Ger.*: Aletris Oligoplex†; Arnica Oligoplex; Capillaron Vertigo; Conva-cyl Ho-Len-Complex; Febro-cyl L Ho-Len-Complex; HanoToxin M; Hanotoxin M; Hepa-Gastreu N R7; Hepar comp; Infi-China; Infi-Symphytum; Infigripp; Infihepan; Jowidarmin; Mato; Milzimmunosyx; Monapax; Nux Vomica N Oligoplex; Pertudoron 1; Rheuma-Pasc; Spasmo-Entoxin; toxi-loges; Ventrigutt M; *Hung.*: Hepeel; PSY-Stabil; *Neth.*: Ailgeno spag; Febrilite; Hepa-Gastreu R7; Infragil; Lymphomyosot; Neurovita; PSY-stabil; Restructa H; *Rus.*: Nux Vom-Plus (Нукс Вом-Плюс); Ruta-Plus (Рута-Плюс); *S.Afr.*: Pertudoron Drops†; *Switz.*: Hepeel; Regenaplex Nr. 35b; Regenaplex Nr. 59b; Silacten; *Ukr.*: Enterocind (Энтерокинд).

Cineole

Cajuputol; Cayeputol; Cineol; Cineolas; Cinéole; Cineolum; Cyneol; Eucaliptol; Eucalyptol (USAN); Eucalyptol; Eucalyptolum; Sineoli; Цинеол.

1,8-Epoxy-*p*-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane.

$C_{10}H_{18}O$=154.3

CAS — 470-82-6.

UNII — RV6J6604TK

NOTE. Do not confuse with Cajuput Oil (p. 2464.1), which has synonyms similar to cajupetol and cayeputol that are used for Cineole.

Description. Cineole is a colourless liquid, with an aromatic camphoraceous odour, obtained from eucalyptus oil, cajuput oil, and other oils.

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

Ph. Eur. 8: (Cineole). A clear colourless liquid. It solidifies at about 0.5 degrees. Practically insoluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Eucalyptol). It is obtained from eucalyptus oil and from other sources. Store in airtight containers.

Profile

Cineole has the actions and uses of eucalyptus oil (p. 2501.2). It has been used in counter-irritant ointments and in dental products. It has also been used in nasal preparations, but oily solutions inhibit ciliary movement and may cause lipoid pneumonia. Preparations containing cineole with other volatile substances have been used in the treatment of renal and biliary calculi.

References.

1. Kehrl W, *et al.* Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial. *Laryngoscope* 2004; 114: 738–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Soledum Balsam; Soledum; *Switz.*: Bronchomed.

Multi-ingredient Preparations. *Arg.*: Aseptobron N; Aseptobron; Aseptobron; Atomo Desinflamante Familiar; Atomo Desinflamante G; Atomo Desinflamante; Bronco Etersan; Di-Neumobron; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; No-Tos Adultos; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Refenax Caramelos Expectorantes; Rowatinex; *Austral.*: Bosisto's Vaporising Ointment†; Euky Bearub; Nasex†; Spray-Tish Menthol; *Austria*: Rhinospray Plus; Rowachol; Rowatinex; Wick SinexAloe; *Belg.*: Eucalyptine Pholcodine; Eucalyptine†; Eucalyptine; Eucalyptine; Eucalyptine; Inhalo Rhinathiol; Inopectol†; Olbas; Pulmex Baby; Pulmex†; *Braz.*: Algice; Angino-Rub; Bromil Grip†; Bromil; Bromil; Fluomint†; Gripsay; Inhalante Yatropan; Ozonyl Aquoso; Ozonyl Expectorante; Ozonyl; Pastilhas Valda†; Penetro; Tetrapulmo†; Transpulmin Balsamo; Transpulmin; Vick Pastilhas†; *Canad.*: Antiseptic Mouthwash; Cal Mo Dol†; Carboseptol†; Demo-Cineol†; Glenalgesic Forte†; Larynsol†; Listerine Antiseptic Tartar Control; Listerine Antiseptic with Fluoride; Listerine; Mielocol†; Naturub; Original Antiseptic Mouthwash†; Orthorub†; Rhino-Vaccin†; *Chile*: Listerine; Oralfresh Citrus†; Oralfresh Clasico†; Rowatinex; *China*: Qie Nuo (切诺); *Cz.*: Rowachol; Rowatinex; *Denm.*: Otrivin Menthol; *Fin.*: Otrivin Menthol; *Fr.*: Bi-Qui-Nol; Dinacode avec codeine†; Essence Algerienne; Eucalyptine Le Brun; Eucalyptine; Eucalyptine; Hexapneumine†; Listerine protection dents et gencives; Listerine Stay White; Neuriplege Sport; Pectoderme†; Pholcones Bismuth; Pulmofluide Simple; Valda†; *Ger.*: Rhinospray Plus; Rowachol; Rowatinex; Transpulmin Balsam†; *Hong Kong*: BF-Analgesic Balm†; Listerine Cool Mint; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; *Hung.*: Rhinospray Plus; Rowachol; Rowatinex; *India*: Aerway; Cool Mint Listerine; Coriminic-Vaporise; Dristan Nasal Drops†; Endrine Mild; Endrine; Genvol Plus; Karvol Plus; Kolq Inhalant; Listerine; Sinarest Vapocaps; *Indon.*: Dactylen; Listerine Coolmint†; Listerine†; Transpulmin BB Balsam; *Irl.*: Rowachol; Rowatinex; *Israel*: Gargol; Rowachol; Rowatinex; *Ital.*: Abiostil; Balsamico; Calyptol; Lipobalsamo; Listerine Fresh Citrus; Listerine Tartar Control; Neo Borocillina Decong; Pumilene Vapo; Rinogutt; Rinovit; Transpulmina Gola; Transpulmina Tosse†; Vicks Sinex; *Malaysia*: Rowachol; Rowatinex; *Mex.*: Bronkitose Mielimon; Cholex; Duais Nordin; Guayalin; Iodex Cristal; Listerine; *Mon.*: Bronchodermine; Bronchodermine; Calyptol; Glyco-Thymoline; *Neth.*: Balsoclase Compositum†; Balsoclase-E†; Otrivin Menthol; Rhinospray met eucalyptus; *Norw.*: Otrivin med mentol; *NZ*: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; Tixylix Chest Rub; Vicks Sinex†; *Philipp.*: Kamillosan M; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar Control; Listerine Teeth & Gum Defense; Rhea Superscent Oil†; Rowachol; Rowatinex; Supercent; Transpulmin Balsam†; *Pol.*: Rowachol; Rowatinex; Salviasept; Terpichol; *Port.*: Transpulmina; Transpulmina; *Rus.*: Nazol Advance (Назол Адванс); Rowatinex (Роватинекс); Sleepex (Слипекс); *S.Afr.*: Respisniffers†; Woodwards Inhalant; *Singapore*: Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; *Spain*: Brota Rectal Balsamico†; Caltoson Balsamico†; Diminex Antitusigeno; Dolmitin†; Eupnol; Mentobox; Pastillas Pectorales Kely†; Pulmofasa; Rinobanedif; Rowachol; Rowanefrin; Sinus Inhalaciones; Vitavox†; *Swed.*: Otrivin Menthol; *Switz.*: Denosol; Mucosan†; Nasobol Inhalo; Onguent aux herbes Keller; Parapic; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; Resorbane; Transpulmin N; Vicks Sinex; *Thai.*: Dexalin Balm; Hot Ize; Rowachol; Rowatinex; Sore Mouth Gel†; *Turk.*: Bugumentol; Bugusan; Buguseptil; Gelocaps; Mentimol†; Mentimol; Mentolin; Mentoseptol; Oka Mentol; Otaci Oka Mentol; Otaci Salvia; Otrivine Mentol; Rinolar; Sulfarhin; *UK*: Dubam; Listerine Antiseptic Mouthwash; Lockets; Nostroline; Nowax; Rowachol; *Ukr.*: Nasol Kids (Назол Кидс); Nazol Advans (Назол Адванс); *USA*: Babee; BFI; Listerine; Nostrilla Conditioning Double Moisture; Pfeiffer's Cold Sore; Rid-a-Pain; Saratoga; Sting-Eze; Toetal Fresh; *Venez.*: Rowachol; Rowatinex; Transmin.

Cinnamedrine *(USAN, rINN)* ⊗

Cinamedrina; Cinnamédrine; Cinnamedrinum; *N*-Cinnamylephedrine; Циннамедрин.

α-{1-[Methyl(3-phenyl-2-propenyl)amino]ethyl}benzenemethanol.

$C_{19}H_{23}NO$=281.4

CAS — 90-86-8.

UNII — Y1245J8012.

Cinnamedrine Hydrochloride *(rINNM)* ⊗

Cinamedrina, hidrocloruro de; Cinnamédrine, Chlorhydrate de; Cinnamedrini Hydrochloridum; *N*-Cinnamylephedrine Hydrochloride; Hidrocloruro de cinamedrina; Циннамедрина Гидрохлорид.

$C_{19}H_{23}NO,HCl$=317.9

UNII — T4B6SPQ0UF.

Profile

Cinnamedrine hydrochloride is reported to have sympathomimetic actions resembling those of ephedrine. It was formerly used with analgesics in the symptomatic relief of dysmenorrhoea.

Cinnamon

Canela; Canela do Ceilão; Cannelle dite de Ceylan; Ceylon Cinnamon; Ceylonzimt; Cinamonu žievė; Cinnam.; Cinnamomi cortex; Cinnamon Bark; Fahéj; Kanel; Kaneli; Skoficovníková kůra; Zimt; Zimtrinde; Корица.

UNII — 5S29HWU6QB.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia*. However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia*. Care should be taken to differentiate between the botanical sources.

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

Ph. Eur. 8: (Cinnamon). The dried bark, freed from the outer cork and the underlying parenchyma, of the shoots grown on cut stock of *Cinnamomum verum* containing not less than 1.2% v/w of essential oil. It has a characteristic, aromatic odour.

The BP 2014 directs that when Powdered Cinnamon is prescribed or demanded, material containing not less than 1.0% v/w of essential oil shall be dispensed or supplied.

Profile

Cinnamon, the bark of *Cinnamomum verum* (*C. zeylanicum*), is carminative and slightly astringent. It is included in some preparations for gastrointestinal disorders and is being studied for its potential as an adjunct in the management of type 2 diabetes mellitus. It is also used as a flavour. It is a source of cinnamon oil (below).

References.

1. WHO. Cortex Cinnamomi. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/12.html (accessed 04/02/10)
2. Dugoua JJ, *et al.* Prom type 2 diabetes to antioxidant activity: a systematic review of the safety and efficacy of common and cassia cinnamon bark. *Can J Physiol Pharmacol* 2007; 85: 837–47.
3. Chase CK, McQueen CB. Cinnamon in diabetes mellitus. *Am J Health-Syst Pharm* 2007; 64: 1033–5.
4. Pham AQ, *et al.* Cinnamon supplementation in patients with type 2 diabetes mellitus. *Pharmacotherapy* 2007; 27: 595–9.
5. Barceloux DG. Cinnamon (*Cinnamomum* species). *Dis Mon* 2009; 55: 327–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Detox Program; Digestive Bitters; Gluco Support; Oil†; *Austria*: Brady's-Magentropfen; China-Eisenwein†; Klosterfrau Melissengeist; Mariazeller; Montana; *Belg.*: Eau Des Carmes; *Braz.*: Balsamo Branco; Paratonico†; *Canad.*: Magen- und Darmtee N†; *Cz.*: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Passedan†; *Fr.*: Afra†; Feminabiane Confort Urinaire; Glycepure; Quintonine†; Santane D_5†; Santane F_{10}†; Santane R_8†; Tavmet; *Ger.*: Amara-Pascoe; Klosterfrau Melissengeist; Melissengeist; Montana N; Schwedentrunk Elixier; Sedovent†; *Hung.*: Klosterfrau Melisana; Montana; *India*: Aptizooom; Eugynin; Koflet; Manix; *Indon.*: Astadiab; Cinula; Oncoxin; *Ital.*: Biophase Shampoo; Dam; *Jpn*: Anchusan; Colgen Maoto; Goreisan; Goshajinkigan; Goshakusan; Hachimijiogan; Inchingoreisan; Ireito; Jidabokuippo; Juzentaihoto; Kakkonto; Kakkontokasenkyushin'i; Keishibukuryogan; Keishibukuryogankayokuinin; Keishikajutsubuto; Keishikaryukotsuboreito; Keishikashakuyakudaioto; Keishikashakuyakuto; Keishininjinto; Keishito; Maoto; Mokuboito; Ninjin'yoeito; Nyoshinsan; Ogikenchuto; Orento; Ryokeijutsukanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saireito; Shakanzoto; Shokenchuto; Shoseiryuto; The Guard Seichojo; Tokakujokito; Tokikenchuto; Tokishigyakukagoshuyushokyoto; Tokito; Unkeito; Yokuininto; *Malaysia*: Taisho Kampo; *Mex.*: Varicyl; *Pol.*: Reumpapai; *Rus.*: Doppelherz Melissa (Доппельгерц Мелисса); Himcolin (Химколин); Wantong Artiplas (Вантонг Артиплас); *S.Afr.*: Melissengeist†; Rooilavental; Spiritus Contra Tussim Drops†; *Spain*: Agua del Carmen; *Switz.*: Baume Zeller; Odontal; Padma Digestin; Tisane pour les problemes de prostate; *Thai.*: Meloids; *Turk.*: Keten; *UK*: Digestion Calming Drops; Melissa Comp.; *Ukr.*: Imunin (Иммунин)†; Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Clinical Nutrients 50-Plus Men; *Venez.*: Aftil; Ocoxin.

Homoeopathic Preparations. *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Vegetal Tonic; *Fr.*: Tonique Vegetal; *Ger.*: Rytesthin; *UK*: Cough Drops.

Pharmacopoeial Preparations

Ph. Eur.: Cinnamon Tincture;

USNF 31: Compound Cardamom Tincture.

Cinnamon Oil

Aetheroleum Cinnamomi Zeylanici; Canela, aceite esencial de; Cinnam. Oil; Esencia de Canela; Essence de Cannelle de Ceylan; Oleum Cinnamomi; Zimtöl; Коричное Масло.

CAS — 8015-91-6.

UNII — E5GY4I6YCZ.

NOTE. In *Martindale*, 'Cinnamon' is used for material obtained from *Cinnamomum verum* and 'Cassia' for material from *Cinnamomum cassia*. However, some of the literature and some pharmacopoeias use the term 'Cinnamon' to describe products from *C. cassia*. Care should be taken to differentiate between the botanical sources.

Pharmacopoeias. *Eur.* (see p. vii) includes oil from both the bark and the leaf of *Cinnamomum verum*.

Jpn under the title Cinnamon Oil specifies oil from either *Cinnamomum cassia* or *Cinnamomum zeylanicum*[*C. verum*].

Cinnamon Bark Oil

Cannelle dite de Ceylan; huile essentielle de; Ceiloninių cinamonų žievės eterinis aliejus; Ceylon Cinnamon Bark Oil; Ceyloni fahéjfakéreg-olaj; Cinnamomi zeylanicii corticis aetheroleum; Cinnamoni Zeylanicii Corticus Aetheroleum; Kaneliöljy; Ceylonin; Kanelolja, ceylonesisk; Silice kůry skořicovníku cejlonského; Коричное Масло Из Коры.
ATC Herb — HA03AW5011 (Cinnamomum verum: *essential oil*); *HA03AW5012* (Cinnamomum verum: *bark*).
UNII — XE54US69EC.

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

Ph. Eur. 8: (Cinnamon Bark Oil, Ceylon). The oil obtained by steam distillation of the bark of the shoots of *Cinnamomum verum*. It contains 55 to 75% of cinnamaldehyde and less than 7.5% of eugenol. A clear, mobile, light yellow liquid becoming reddish over time, with a characteristic odour of cinnamaldehyde. Store in well-filled airtight containers. Protect from heat.

Cinnamon Leaf Oil

Cannelier dit de Ceylan (feuille de), huile essentielle de; Ceiloninių cinamonų lapų eterinis aliejus; Ceyloni fahéjfalevél-olaj; Cinnamomi Zeylanici Folii Aetheroleum; Cinnamomi Zeylanici Folii Etheroleum; Kanelbladolja, ceylonesisk; Kanelinlehtiöljy, Ceylonin; Ol. Cinnam. Fol; Silice listu skořicovníku cejlonského; Коричное Масло Из Листьев.
UNII — S92U8SQ71V.

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

Ph. Eur. 8: (Cinnamon Leaf Oil, Ceylon). The oil obtained by steam distillation of the leaves of *Cinnamomum verum*. It contains less than 3% of cinnamaldehyde, and 70 to 85% of eugenol. A clear, mobile, reddish brown to dark brown liquid, with a characteristic odour of eugenol. Store in well-filled airtight containers. Protect from heat.

Profile

Cinnamon bark oil has properties and uses similar to those of cinnamon (p. 2479.3). It is also included in preparations for musculoskeletal and joint disorders and for respiratory-tract disorders. There have been reports of hypersensitivity to cinnamaldehyde and other constituents of cinnamon oil. Cinnamon leaf oil has also been used, although the amounts of eugenol and cinnamaldehyde are different from the bark oil. Cinnamon bark or leaf oil is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Tiger Balsam Rot; ***Canad.***: Amol†; DSO Dressing; Melisana†; Tiger Balm Red; Tiger Balm Ultra; ***Chile***: Agua del Carmen; Agua Melisa Carminativa; ***Cz.***: Amol; ***Fr.***: Aromasol; Aromavital†; Dida; Esculape†; Gouttes aux Essences; Oliosepti Nez-Gorge; Resistim; Stomargil; Tigre de Chine; Tigridol; ***Ger.***: Amol Heilkrautergeist N; esto-gast; Melissengeist; Salviathymol N; Verdauungstropfen Gastrofunkten†; ***Hong Kong***: Magesto; ***Hung.***: Amol; Carmol; Cholasyl; Tiger Balm Red; ***India***: Aniwel DPS; Aquadil-P; Artrex; Bestozyme P; Carmicide; Cartigen; Catalyd; Catazyme; Collwell; Digeplex; Dorzy DPS; Everzyme; Gastrozyme; Gastrozyme; Hanzyme; Lavazyme; Litzyme; Merispas; Sensur; Sensur; Vitazyme; ***Indon.***: Corsabalm; ***Irl.***: Tiger Balm Red; ***Israel***: Karvol; ***Ital.***: Relaxcol; Valda Propoli†; ***NZ***: Karvol; ***Pol.***: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; ***Rus.***: Efcamon (Эфкамон); ***S.Afr.***: Enterodyne†; Karvol†; ***Singapore***: Karvol; ***Spain***: Depurativo Richelet†; ***Switz.***: Baume du Tigre rouge; Echinarom; Pirom; Spagyrom; ***Thai.***: Caryopin; Magesto; Mesto-Of; ***UK***: Slippery Elm Stomach Tablets.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture; Compound Cardamom Tincture; Concentrated Cinnamon Water; Tolu-flavour Solution.

Citicoline *(pINN)*

CDP-Choline; Citicolina; Citicolinum; Citidoline; Cytidine Diphosphate Choline; Cytidine diphosphocholine; Cytidyl Diphosphocholine; IP-302; Цитиколин.
Choline cytidine-5′-pyrophosphate.
$C_{14}H_{26}N_4O_{11}P_2$=488.3
CAS — 987-78-0.
ATC — N06BX06.
ATC Vet — QN06BX06.
UNII — 536BQ2JVCZ.

Citicoline Sodium *(USAN, pINNM)*

Citicolina sódica; Citicoline Sodique; Natrii Citicolinum; Sodium Citicoline; Sodium Cytidine Diphosphate Choline; Натрий Цитиколин.
Cytidine 5′-(sodium 3′-[2-(trimethylammonio)-ethyl] hydrogen diphosphate), inner salt.
$C_{14}H_{25}N_4NaO_{11}P_2$=510.3
CAS — 33818-15-4.
UNII — 7XQ5AKD9YD.

Pharmacopoeias. In *Chin.*

Profile

Citicoline is a derivative of choline and cytidine that is involved in the biosynthesis of lecithin. It is claimed to increase blood flow and oxygen consumption in the brain and has been given in the treatment of cerebrovascular disorders (including ischaemic stroke, p. 1269.2), parkinsonism, and head injury. It is given by intravenous or intramuscular injection in doses of up to 1 g daily or orally in divided doses of 200 to 600 mg daily.

Citicoline sodium has also been used.

References.
1. Secades JJ, Lorenzo JL. Citicoline: pharmacological and clinical review, 2006 update. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl B): 1–56.
2. Anonymous. Citicoline. *Altern Med Rev* 2008; **13**: 50–7.

Cerebrovascular disorders. Citicoline has shown some short- to medium-term benefit for disturbances of memory and behaviour associated with cerebrovascular disorders.[1]

1. Floravanti M, Yanagi M. Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 09/05/06).

Strabismus. Experimental studies have shown that centrally-acting drugs such as citicoline may improve vision in patients with amblyopia (see Strabismus, p. 2000.3). However, their role in clinical practice is unknown.[1]

1. Chatzistefanou KI, Mills MD. The role of drug treatment in children with strabismus and amblyopia. *Paediatr Drugs* 2000; **2**: 91–100.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Complegel Novo; Nimo-Somazina; Reagin; Somazina; ***Austria***: Startonyl; ***Braz.***: Somazina; ***Chile***: Somazina; ***China***: Ai Xing Dan (爱星丹); Ao Ge Er (奥格尔); Bin Shu (滨舒); Bo Lang Rui Ning (博朗瑞宁); Chen Wang (辰旺); De Yi Rong (德益荣); Feng Hai Qing (丰海清); Jia Jian (加简); Jie Wei Su (洁维苏); Jiu An Suxin (久安苏欣); Lan Gui (兰桂); Li Shu (理枢); Li Tuo Gan (立拓感); Nicholin (尼可林); Ou Mai (欧迈); PiDi Ming (彼迪明); Pu Mei La Tai (普美拉泰); Sai Li Ao (赛立奥); Shu Mo Ta (舒莫它); Si Kao Lin (思考林); Si Ke Lin (思可林); Su Bu Lin (苏布林); Xian Li Ke (先立科); Xin Ke Lai (欣可来); Xin Tong (鑫通); Yi Dan (亿丹); Yi Luo Qing (益落清); You Xin (友欣); ***India***: Ceham; Citilin; Citinova; Clinaxon; Col; Costrok; Inticol; Mycostar; Neocit; Neurospark; Onlyciti; ***Indon.***: Beclov; Brainact; Brainolin; Bralin; Cercul; Cholimed; Cholinaar; Cibren; Citicholine; Crolin; Incelin; Lancolin; Neuciti; Neulin; Neurolin; Nicholin; Recolin; Serfac; Simciti; Soholin; Strolin; Takelin; Zeufor; ***Ital.***: Brassel; Cebroton†; Cidilin; Difosfocin; Gerolin; Logan; Neurex; Neuroton; Nicholin†; Nicolsint; Sintoclar; ***Jpn***: Nicholin; ***Mex.***: Onquevit; Somazina; Zunun; ***Philipp.***: Cholinerv; Citilin; Nicholin; Somazine; Zynapse; ***Port.***: Hipercol; Somazina; Startonyl; Trausan; ***Rus.***: Ceraxon (Цераксон); ***Spain***: Numatol; Somazina; ***Thai.***: Somazina; ***Ukr.***: Ceraxon (Цераксон); Neuroxon (Нейроксон); Somazina (Соматина); ***Venez.***: Somazina.

Multi-ingredient Preparations. ***Arg.***: Nimodilat Plus; Nimoreagin; Nivas Plus; Reagin Vascular; ***China***: Ying Di Te (英迪特); ***Fr.***: Cebrolux; ***India***: Nervijen-CT; Nutam Plus; ***Ital.***: Cebrolux.

Citral

Cytral; Цитраль.
3,7-Dimethyl-2,6-octadienal.
$C_{10}H_{16}O$=152.2
CAS — 5392-40-5 (citral); 141-27-5 (geranial); 106-26-3 (neral).
UNII — T7EU0O9VPP.

Profile

Citral is a terpenoid constituent of lemon oil (p. 2543.1), lemon grass oil (p. 2543.2), melissa oil (p. 2553.2), and many other essential oils; it exists as 2 isomers, *trans*-citral (geranial) and *cis*-citral (neral). It has been used in preparations for respiratory-tract, musculoskeletal, and other disorders. It is also used as a flavour and perfume.

Hypersensitivity. References.

1. Heydom S, *et al.* Citral a fragrance allergen and irritant. *Contact Dermatitis* 2003; **49**: 32–6.
2. Lalko J, Api AM. Citral: identifying a threshold for induction of dermal sensitization. *Regul Toxicol Pharmacol* 2008; **52**: 62–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Fr.***: Bronchorectine au Citral.

Anhydrous Citric Acid

Acidum Citricum; Acidum Citricum Anhydricum; Cítrico anhidro, ácido; Citrinų rūgštis, bevandenė; Citrique (acide) anhydre; Citronensäure; Citronsyra, vattenfri; E330; Kyselina citronová; Sitruunahappo, vedetön; Vízmentes citromsav; Лимонная Кислота Безводная.
2-Hydroxypropane-1,2,3-tricarboxylic acid.
$C_6H_8O_7$=192.1
CAS — 77-92-9.
ATC — A09AB04.
ATC Vet — QA09AB04.
UNII — XF417D3PSL.

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

Ph. Eur. 8: (Citric Acid, Anhydrous). Colourless crystals or granules or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol.

USP 36: (Anhydrous Citric Acid). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Citric Acid Monohydrate

Ácido del Limón; Acidum Citricum Monohydricum; Cítrico monohidrato, ácido; Citrinų rūgštis monohidratas; Citrique (acide) monohydraté; Citromsav-monohidrát; Citronensäure-Monohydrat; Citronsyramonohydrat; Hydrous Citric Acid; Kwas cytrynowy jednowodny; Kyselina citronová monohydrát; Sitruunahappomonohydraatti; Лимонная Кислота Моногидрат.
$C_6H_8O_7,H_2O$=210.1
CAS — 5949-29-1.
ATC — A09AB04.
ATC Vet — QA09AB04.
UNII — 2968PHW8QP.

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

Ph. Eur. 8: (Citric Acid Monohydrate). Efflorescent, colourless crystals or granules, or a white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Citric Acid Monohydrate). Colourless, translucent crystals, or a white, granular to fine, crystalline powder. It is efflorescent in dry air. Soluble 1 in 0.5 of water, 1 in 2 of alcohol, and 1 in 30 of ether. Store in airtight containers.

Uses and Administration

Citric acid is used in effervescing mixtures; the monohydrate is used in the preparation of effervescent granules.

Citric acid monohydrate is used as a synergist to enhance the efficacy of antoxidants.

Preparations containing citric acid are used in the management of dry mouth (p. 2175.3) and to dissolve renal calculi, alkalinise the urine, and prevent encrustation of urinary catheters. Citric acid is an ingredient of citrated anticoagulant solutions. Citric acid has also been used in preparations for the treatment of coughs, gastrointestinal disturbances, and metabolic acidosis.

Adverse Effects and Precautions

Citric acid ingested frequently or in large quantities may cause erosion of the teeth and have a local irritant action.

Interactions

Aluminium hydroxide. Intestinal absorption of aluminium ions may be enhanced by oral doses of citrates. Caution is needed in patients with chronic renal disease receiving aluminium hydroxide as a phosphate binder who are given a calcium supplement in the form of effervescent tablets that contain citric acid.[1]

1. Mees EJD, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59**: 322.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Urologic G; ***Gr.***: Citrolithin; ***India***: Revici; ***Mex.***: Lipocinetic†; ***Pol.***: Citrolyt; ***S.Afr.***: Crystacit; ***Venez.***: Policitra.

Multi-ingredient Preparations. ***Arg.***: Alikal; Alka-Seltzer Doble Accion; Azodac; Fegalgina; Sal de Fruta Eno; Uvasal; ***Austral.***: Alka-Seltzer; Citralite†; Citravescent; Eno; Gastrolyte; PicoPrep;

Ural; *Austria*: Alka-Seltzer; Blanel; Helo-acid; Kalloral; *Braz.*: Alka-Seltzer; Control†; Digestbem; Emidrat; Estomazil; Sadol†; Sal de Andrews; Sal de Pruta Eno; Sonrisal; *Canad.*: Alka-Seltzer; Bromo Madelon†; Enfalyte; Pico-Salax; Picodan; Purg-Odan; *Chile*: Distruta; Penokomp 39; Kanacitrin; Sal de Pruta Eno; Uroalquine; Yasta; *Cz.*: Alka-Seltzer; Blemaren N; Carbocit; Herbadent; Picoprep; *Denm.*: CitraFleet; Picoprep; Samarin; *Fin.*: Alka-Seltzer†; CitraFleet; Picoprep; *Fr.*: Actigess†; Alhydrate†; Alka-Seltzer; Bactigyn; CitraFleet; Citrocholine†; Fanolyte; Hepargitol; Hydrigoz†; Novalac Hydranova; Picolite; Picoprep; *Ger.*: Alka-Seltzer; Blemaren N; CitraFleet; Pepzitrat†; Picoprep; Retterspitz Ausserlich; Retterspitz Innerlich; Weleda Heuschnupfenspray; *Gr.*: E-Z-Gas; Gastrovison; *Hong Kong*: Alka-Seltzer†; Eno†; Picolax; *Hung.*: Alka-Seltzer; Blemaren N; E-Z-Gas; Egaver Plusz; Egaver; Picoprep; *India*: Ableed; Alkacos; Alkamax; Alkasym; Carmicide; Citro-Soda; Distone; Dristan Expectorant; Icey; K-Cit; Kezar; Kufma; Manzer; Maxoza; Merispas; Oralka-K; Orfix; Urisoda; *Indon.*: Koffex for Children; Promethazine Ikapharmindo; *Irl.*: Alka-Seltzer; Andrews; CitraFleet; Cymalon; Lemsip Dry Cough; Picolax; Rehidrat†; Resolve†; *Israel*: E-Z-Gas II; Minerali; Pico-Salax; Urikal; *Ital.*: Alka-Seltzer; Citroepatina†; Citromagnesiaca; Duogas; Geffer; Lavanda Sofar; *Malaysia*: Alka-Seltzer; Ezee; pH Care; Picoprep†; Potcit; U-Lite; Ural; Urisoda; *Mex.*: Kaposalt; Urodasio NF; *Mon.*: Poncitril; *Neth.*: Alka-Seltzer; Gastrogas†; Picoprep; *Norw.*: CitraFleet; Picoprep; *NZ*: Alka-Seltzer; Picoprep; Ural; *Philipp.*: Alka-Seltzer†; Ural; *Pol.*: Citropepsin; *Port.*: CitraFleet; Creme Laser Hidrante†; Detoxergon; Eno†; *Rus.*: Alka-Seltzer (Алка-Зельтцер); Blemaren (Блемарен); Limontar (ЛИМОНТАР); *S.Afr.*: Adco-Sodasol; Alkafizz; Citro-Soda; Effersol; Picoprep†; Pneucid†; Quatro-Soda; Uri-Alk; Vicks Cough Syrup†; *Singapore*: Alka-Seltzer; Bio-Tachest†; Citravescent; Dicitrate; K-Mix; Potcit; Uricalm; *Spain*: Cardi-Braun; Citorsal; CitraFleet; Juistegas; Sal de Pruta Eno; Uralyt Urato; *Swed.*: Alka-Seltzer†; CitraFleet; Picoprep; Renapur; Samarin; Samarin; *Switz.*: Alka-Seltzer; E-Z-Gas II; Picoprep; Siesta-1; *Thai.*: Alka-Seltzer; Polyvit; *Turk.*: Alka-Seltzer; Historan; *UK*: Alka-Seltzer XS; Alka-Seltzer; Allens Junior Cough; Andrews; Carbex; Cymalon; Effercitrate; Eno; Entrocalm Replace; Hill's Balsam Chesty Cough for Children; Lemsip Cough & Cold Dry Cough; O.R.S.; Oralyte; Potters Children's Cough Pastilles; Resolve; Uriflex G; Uriflex R; Uro-Tainer Solution R; Uro-Tainer Suby G; Zubes Blackcurrant; Zubes Honey & Lemon; *Ukr.*: Alka-Seltzer (Алка-Зельтцер); Blemaren (Блемарен); Citramon Forte (Цитрамон-Форте); *USA*: Alka-Seltzer Antacid; Alka-Seltzer Heartburn Relief; Alka-Seltzer with Aspirin; Alka-Seltzer; Bicitra†; Bromo Seltzer Effervescent Granules†; Cytra-2; Cytra-3; Cytra-K; Cytra-LC†; E-Z-Gas II; Extra Strength Alka-Seltzer Effervescent Tablets; Gold Alka-Seltzer; Lycelle; Oracit; Original Alka-Seltzer Effervescent Tablets; Prepopik; Renacidin; Resol; SalivaSure; Sparkles; Taron; Zee-Seltzer; *Venez.*: Alka-Seltzer; Eno.

Homoeopathic Preparations. *Canad.*: Ubicoenzyme; *Ger.*: Citro-kehl; HanoOxygen E; Zitronensaurezyklus-Heel.

Pharmacopoeial Preparations

BP 2014: Lemon Syrup; Paediatric Compound Tolu Linctus; Paediatric Simple Linctus; Potassium Citrate Mixture; Simple Linctus;

Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);

USP 36: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation; Magnesium Carbonate and Citric Acid for Oral Solution; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; Magnesium Citrate Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Sodium Citrate and Citric Acid Oral Solution; Tricitrates Oral Solution.

Citronella Oil

Citrinžolių eterinis aliejus; Citronela, aceite esencial de; Citronellae Aetheroleum; Citronellae Etheroleum; Citronellaolaj; Citronellöl; Citronellolja; Citronelová silice; Citronnelle, huile essentielle de; Esencia de citronela; Oleum Citronellae; Sitronellaöljy; Цитронеллое Масло.

UNII — QYO8Q067D0.

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

Ph. Eur. 8: (Citronella Oil). The oil obtained by steam distillation from the fresh or partially dried aerial parts of *Cymbopogon winterianus*. It contains 30.0 to 45.0% citronellal, 9.0 to 15.0% citronellol, 2.0 to 4.0% citronellyl acetate, less than 2.0% geranial, 20.0 to 25.0% geraniol, 3.0 to 8.0% geranyl acetate, 1.0 to 5.0% limonene, and less than 2.0% neral. A pale yellow to brownish-yellow liquid with a very strong odour of citronellal. Store in well-filled containers. Protect from light.

Profile

Citronella oil is used as a perfume and insect repellent. It is also used in aromatherapy. Hypersensitivity has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aulo Gelio Repelente; Aulo Gelio Toallitas; Exilet; Moscut; Rep Repelente; *Malaysia*: Moz-Away; *UK*: Mozzie Patch; Natrapel.

Multi-ingredient Preparations. *Arg.*: Aulo Repelente De Piojos; Max Repel; Max Repel; Rep Locion Repelente; Rep Repelente; *Austral.*: Apex Repel Natural; *Belg.*: Mouskito Travel Stick; *Canad.*: Natrapel Plus; *Cz.*: Amol; *Fr.*: Ephydrol; Ysol 206†; *Ger.*: esto-gast; Melissengeist; *Hung.*: Carmol; *Indon.*: Corsabalm; *Ital.*: Citrosystem; Mistick Verde; Pungino; *Mon.*: Akipic; *Pol.*: Carmolis; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); *S.Afr.*: Melissengeist†; *Switz.*: Baume du Chalet; Novital; *UK*: Repelselect; Snowfire; *USA*: Treo.

Clivers

Amor de hortelano; Azotalenguas; Bardana; Cleavers; Galii Aparinis Herba; Galium; Goosegrass; Presera; Липушник.

UNII — Z4B6561488.

Profile

Clivers is the dried aerial parts of *Galium aparine* (Rubiaceae). It has been used in herbal medicine, mainly as a diuretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: DermaCo; *UK*: Antitis; Aqua Ban Herbal; Athera; Backache; Boots Water Relief; Cascade; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kas-Bah; Modern Herbals Menopause; Modern Herbals Water Retention; Napiers Herbal Slimming Aid; Psorasolv; Quantrim Herbal Slimming Tablets; Sciargo; Skin Cleansing; Slimwell Herbal Slimming Tablets; Tabritis; Water Naturtabs; Watershed; *Ukr.*: Tazalok (Тазалок).

Homoeopathic Preparations. *Canad.*: Cutisitum†; Essigen†; Itires; Toxex; Tyglan†; Visceel†; Yellow Dock Combination†; *Cz.*: Galium; *Hung.*: Toxex; *Neth.*: Toxex.

Cloprostenol Sodium *(BANM, USAN, rINNM)*

Cloprostenol sódico; Cloprosténol Sodique; Cloprostenoli natricum; ICI-80996; Natrii Cloprostenolum; Натрий Клопростенол.

Sodium (±)-(Z)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(*E*)-(3*R*)-4-(3-chlorophenoxy)-3-hydroxybut-1-enyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

$C_{22}H_{35}ClNaO_6$=446.9

CAS — 40665-92-7 (cloprostenol); 55028-72-3 (cloprostenol sodium).

UNII — 886SAV9675.

Pharmacopoeias. In *BP(Vet)* and *US* for veterinary use only.

BP(Vet) 2014: (Cloprostenol Sodium). A white or almost white amorphous hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in acetone. Protect from light and moisture.

USP 36: (Cloprostenol Sodium). A white or almost white, amorphous hygroscopic powder. Freely soluble in water, in alcohol, and in methyl alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light.

Profile

Cloprostenol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). The sodium salt is used as a luteolytic in veterinary medicine. It should be used with caution as it is reported to be readily absorbed through the skin.

Clove

Caryoph.; Caryophylli Flos; Caryophyllum; Clavo; Clou de girofle; Cloves; Cravinho; Cravo-da-Índia; Gewürznelke; Gewürznelken; Girofler; Gvazdikėlial; Hřebíčkovcový květ; Kryddnejlika; Mausteneilikka; Szegfűszeg; Tropical Myrtle; Гвоздика.

ATC Herb — HA03AW5056 (Syzygium aromaticum: flower bud).

UNII — K48IKT5321.

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

Ph. Eur. 8: (Clove). The whole flower buds of *Syzygium aromaticum* (*Eugenia caryophyllus*), containing not less than 15% v/w of volatile oil, dried until they become reddish-brown, and with a characteristic aromatic odour. Protect from light.

The BP 2014 directs that when Powdered Clove is prescribed or demanded, material containing not less than 12.0% v/w of essential oil shall be dispensed or supplied.

Uses and Administration

Clove is a carminative and is used as a flavour. It is the source of clove oil (below).

Clove and clove oil have been abused in the form of cigarettes.

Adverse Effects

Abuse. Smoking of cigarettes composed of a mixture of tobacco and cloves (kretek) is a habit that originated in Indonesia and has spread to other countries including the UK and the USA. There have been reports of severe and sometimes fatal respiratory illness related to smoking clove cigarettes and there is also evidence from *animal* studies that clove cigarette smoke and eugenol (the principal constituent of clove oil) have harmful pulmonary effects. The Council on Scientific Affairs of the American Medical Association considers that in addition to the hazards associated with smoking tobacco, clove cigarettes may also produce severe lung injury in certain susceptible individuals and could also induce pulmonary aspiration in healthy individuals due to diminution of the gag reflex produced by the local anaesthetic action of eugenol.[1] The American Academy of Pediatrics has also alerted paediatricians in the USA to clove-cigarette smoking by young people and warned of the risks.[2]

1. American Medical Association Council on Scientific Affairs. Evaluation of the health hazard of clove cigarettes. *JAMA* 1988; 260: 3641–4.
2. Committee on Substance Abuse. Hazards of clove cigarettes. *Pediatrics* 1991; 88: 395–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Klosterfrau Melissengeist; Mariazeller; Pervivo; *Belg.*: Eau Des Carmes; *Braz.*: Balsamo Branco; Vitonico; *Canad.*: Clear Capsules†; Intestinal Bulking Agent II†; Kalenite†; Para-Gone; Special Formula Bulking Agent†; *Cz.*: Klosterfrau Melisana; *Fr.*: Dida; Saugella Homme; *Ger.*: Klosterfrau Melissengeist; Melissengeist; *Hung.*: Bittner; Klosterfrau Melisana; *India*: Abana; Bugynin; Fortege; Pallrywyn Forte; *Ital.*: Biophase Shampoo; Saugella Uomo; *Jpn*: Cabe 2 New; Jidabokuippo; Nyoshinsan; *Pol.*: Padma 28; Pervivo; *Rus.*: Doppelherz Melissa (Допмельгерц Мелисса); Maraslavin (Мараславин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Clairo†; Melissengeist†; Spiritus Contra Tussim Drops†; *Singapore*: Stop Snoring; *Switz.*: Arteria-vita; Kernosan Eau Dentifrice†; Odontal; Padmed Circosan; Tisane pour les problemes de prostate; *UK*: Melissa Comp.; Padma 28; Padma Circosan; Revitonil; *Ukr.*: Imunin (Иммунин)†; Normoton (Нормотон); Olesan (Олесан); Trypsidan (Трипсидан)†.

Homoeopathic Preparations. *UK*: Cough Drops; Laxadoron.

Clove Oil

Caryophylli floris aetheroleum; Caryophylli Floris Etheroleum; Clavo, aceite esencial de; Clou de girofle, huile essentielle de; Esencia de Clavo; Essence de Girofle; Gvazdikėlių eterinis aliejus; Neilikkaöljy; Nejlikolja; Nelkenöl; Ol. Caryoph.; Oleum Caryophylli; Silice hřebíčkovcového květu; Szegfűszegolaj; Гвоздичное Масло.

ATC Herb — HN01BW5001 (Syzygium aromaticum: essential oil); HA03AW5055 (Syzygium aromaticum: essential oil); HA01WC5005 (Syzygium aromaticum: essential oil).

UNII — 578389D6D0.

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

Ph. Eur. 8: (Clove Oil). A clear yellow liquid obtained by steam distillation from clove containing 75.0 to 88.0% of eugenol. It becomes brown on exposure to air. Miscible with dichloromethane, with toluene, and with fatty oils. Store in well-filled airtight containers. Protect from light and heat.

USNF 31: (Clove Oil). The volatile oil distilled with steam from clove. It contains not less than 85.0% of phenolic substances, chiefly eugenol. Soluble 1 in 2 of alcohol (70%). Store in well-filled airtight containers.

Incompatibility. PVC bottles softened and distorted fairly rapidly in the presence of clove oil, which should not be stored or dispensed in such bottles.[1]

1. Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; 210: 100.

Uses and Administration

Clove oil is a carminative that is sometimes used in the treatment of flatulent colic. It is also used as a flavour.

Applied externally clove oil is irritant but can produce local anaesthesia. It is used as a domestic remedy for toothache, a plug of cotton wool soaked in the oil being inserted in the cavity of the carious tooth; repeated application may damage the gingival tissues. Mixed with

zinc oxide, it is used as a temporary anodyne dental filling, although eugenol (p. 2501.3), one of its constituents, is often preferred. Clove oil is included as a counter-irritant in preparations for musculoskeletal and joint disorders. It is also used in aromatherapy.

Adverse Effects

The eugenol present in clove oil may act as an irritant to skin and mucous membranes; it may also cause hypersensitivity. For references to the adverse effects of clove oil abused in the form of cigarettes, see under Clove p. 2481.3.

Poisoning. Severe toxicity after ingestion of clove oil by young children has been reported.[1-4] Adverse effects included coma, acidosis, a generalised seizure, disordered blood clotting, and acute liver damage.

1. Lane BW, *et al.* Clove oil ingestion in an infant. *Hum Exp Toxicol* 1991; 10: 291–4.
2. Hartnoll G, *et al.* Near fatal ingestion of oil of cloves. *Arch Dis Child* 1993; 69: 392–3.
3. Eisen JS, *et al.* N-acetylcysteine for the treatment of clove oil-induced fulminant hepatic failure. *J Toxicol Clin Toxicol* 2004; 42: 89–92.
4. Janes SE, *et al.* Essential oil poisoning: N-acetylcysteine for eugenol-induced hepatic failure and analysis of a national database. *Eur J Pediatr* 2005; 164: 520–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Naeltjie-Olie; *UK*: Dentogen; Soothake Toothache Gel.

Multi-ingredient Preparations. *Austral.*: Herbal Throat Spray; Oral-Eze; Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; Wormwood Complex; *Austria*: Parodontax†; Tiger Balsam Rot; Tiger Balsam Weiss; *Braz.*: Dentisan†; *Canad.*: Amol†; DSO Dressing; External Anti-Pain Oil†; Muscle Mist; Tiger Balm Arthritis Rub; Tiger Balm Red; Tiger Balm Ultra; Tiger Balm White; Wonder Oil; *Chile*: Agua del Carmen; Agua Melisa Carminativa; *Cz.*: Amol; Herbadent; Stopangin; *Fr.*: Arnicadol†; Aromasol; Aromavital†; Baume Aroma; Capsaine; Esculape†; Gouttes aux Essences; Nazinette du Docteur Gilbert; Percutalgin'Phyto; Tigre de Chine; Tigridol; *Ger.*: Amol Heilkrautergeist N; esto-gast; Melissengeist; Repha-Os†; Salviathymol N; Tiger Balm weiss; Verdauungstropfen Gastrofunkten†; *Gr.*: Tiger Balm; *Hong Kong*: Magesto; *Hung.*: Amol; Carmol; China-Balsam; Gingisol; Hustagil Anticold Cream; Tiger Balm Red; Tiger Balm White; *India*: Arowash†; Olesan Oil; Sensur; Sensur; *Indon.*: Balsam Sakti†; Corsabalm; *Irl.*: Olbas; Olbas; Soothake Toothache Tincture; Tiger Balm Red; Tiger Balm White; *Israel*: Tiger Balm Red; Tiger Balm White; *Ital.*: Dentosan Azione Intensiva; Dentosan Mese; Fialetta Odontalgica Dr Knapp; *Neth.*: Olbas†; *NZ*: Electric Blue Headlice; Electric Blue Headlice; *Pol.*: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; Olbas; Olbas; Salviasept; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Efcamon (Эфкамон); *S.Afr.*: Alpha Toothache Essence†; Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Enterodyne†; Helmontskruiet†; Moultons Pain Paint†; Muscle Rub†; Prep†; Puma Balm; SB Toothache Drops†; *Singapore*: Teenstick; *Spain*: Otogen Calmante; *Switz.*: Baume du Tigre blanc; Baume du Tigre rouge; Echinarom; Olbas; Spagyrom; *Thai.*: Caryopin; Magesto; Masaga; Mesto-Of; *Turk.*: Disinol; Piyraleks; Sena-Oil; *UK*: Hactos; Nine Rubbing Oils; Olbas for Children; Olbas; Olbas; Potters Sugar Free Cough Pastilles; Red Oil; Repelselect; Snowfire; Soothake Toothache Tincture; Teenstick; Tiger Balm; *Ukr.*: Stopangin (Стопангин); *USA*: Dentapaine; Tiger Balm; Toothache Gel.

Homoeopathic Preparations. *UK*: Medicinal Gargle.

Pharmacopoeial Preparations
BP 2014: Aromatic Cardamom Tincture.

Red Clover

Cow Clover; Meadow Clover; Purple Clover; Trébol rojo; Trefoil; Красный Клевер; Луговой Клевер.
UNII — L9153EKV2Y.

Pharmacopoeias. In *US*, which also includes the powdered form and powdered extract.

USP 36: (Red Clover). The dried inflorescence of *Trifolium pratense* (Fabaceae). It contains not less than 0.5% of isoflavones, calculated on the dried basis as the sum of daidzein (p. 2620.3), genistein (p. 2620.3), formononetin, and biochanin A. Protect from light and moisture.

Profile

The flowerheads of red clover have been used in herbal medicine. The isoflavones present in red clover have been investigated, similarly to other phytoestrogens, for their potential endocrine effects.

References.

1. Booth NL, *et al.* Clinical studies of red clover (Trifolium pratense) dietary supplements in menopause: a literature review. *Menopause* 2006; 13: 251–64.
2. Coon JT, *et al.* *Trifolium pratense* isoflavones in the treatment of menopausal hot flushes: a systematic review and meta-analysis. *Phytomedicine* 2007; 14: 153–9.
3. Sabudak T, Guler N. Trifolium L. a review on its phytochemical and pharmacological profile. *Phytother Res* 2009; 23: 439–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Promensil; Trinovin; *Braz.*: Climadil; Clinet; Promensil; *Canad.*: Promensil; *Indon.*: Promeno; Trinovin; *Singapore*: Pem-E; *UK*: Menoflavon; Promensil; *Ukr.*: Kleverol (Клеверол).

Multi-ingredient Preparations. *Austral.*: Bone Complex; FemiNan; Mens Super Soy/Clover†; PM Meno-Care; Soy Power Plus†; *Canad.*: Libeeda for Women; *Indon.*: Femosa; Fitogen; Osteopor; *Ital.*: Bioestril Ginseng; Bioestril Valeriana; Ginepausil; *Philipp.*: Nutrafem; Thinber Fiber Complex†; *Rus.*: Cedoflor (Седофлор); Sedativae Species No 3 (Седативный Сбор 3); *Spain*: Fitogyn; Soyred†; *Switz.*: Metabol; *UK*: Napiers Oral Skin Soother Herbal Relief; *USA*: Detox.

Homoeopathic Preparations. *Canad.*: Essigen†; Yellow Dock Combination†.

Pharmacopoeial Preparations
USP 36: Red Clover Tablets.

Cnicus Benedictus

Blessed Thistle; Cardo bendito; Cardo Santo; Centáurea bendita; Centáurea Sudorífica; Chardon Bénit; Holy Thistle; Kardobenediktenkraut; Кникус Аптечный.
ATC Herb — HA09WA5010 (Cnicus benedictus herb).
UNII — 6LSZL09795 (Cnicus benedictus); NJN80GZ34N (Cnicus benedictus flowering top).

Profile

Cnicus benedictus, the flowering tops of *Cnicus benedictus* (*Carbenia benedicta; Carduus benedictus*) (Compositae), has been used as a bitter.

Homoeopathy

Cnicus benedictus has been used in homoeopathic medicines under the following names: Carduus benedictus; Carduus ben.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Mariazeller; Pervivo; *Ger.*: Gallexier; Gastritol; *Hung.*: Bittner; *Pol.*: Artecholin†; Artecholwex†; Pervivo; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Essens Amara of Groen Amara; *Switz.*: Gastrosan; Kernosan 24; Kernosan 26; *UK*: Bio-Strath Artichoke Formula; Sure-Lax (Herbal); *Ukr.*: Gastritol (Гастритол); Hepahealth (Гепахелс).

Homoeopathic Preparations. *Ger.*: Heweberberol; Rufebran heparo†; *USA*: Preferred Remedies Detoxin.

Cobalt

Cobalto; Cobaltum; Kobalt; Кобальт.
Co=58.933195
CAS — 7440-48-4.
UNII — 3G0H8C9362.

Cobalt Chloride

Cloruro cobaltoso; Cobalto, cloruro de; Cobaltous Chloride; Kobaltu(II) chlorek; Хлористый Кобальт.
$CoCl_2.6H_2O$=237.9
CAS — 7646-79-9 (anhydrous cobalt chloride); 7791-13-1 (cobalt chloride hexahydrate).
UNII — EVS87XF13W (cobalt chloride); 17AWG63ZBC (cobalt chloride hexahydrate).

Cobalt Oxide

Cobalto, óxido de; Óxido cobaltoso-cobáltico; Tetraóxido de tricobalto; Tricobalt Tetroxide; Кобальт Оксид; Окись Кобальта.
Co_3O_4=240.8
CAS — 1308-06-1.
UNII — U5K772NS56.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Cobalt Oxide). It consists of cobalt (II, III) oxide (tricobalt tetroxide) with a small proportion of cobalt (III) oxide (dicobalt trioxide). A black powder. Practically insoluble in water; dissolves in mineral acids and in solutions of alkali hydroxides.

Uses and Administration

Cobalt is a trace mineral required in the synthesis of vitamin B_{12} and compounds such as the acetate, gluconate, sulfate, and sodium gluconate have sometimes been included in dietary supplements. Although it has been reported that cobalt chloride can produce reticulocytosis and raise the erythrocyte count such use in the treatment of anaemias has been deprecated.

In veterinary medicine various cobalt salts are given to ruminants as a dietary supplement.

Adverse Effects

Reactions to cobalt have included anorexia, nausea and vomiting, diarrhoea, precordial pain, cardiomyopathy, flushing of the face and extremities, rashes, tinnitus, temporary nerve deafness, renal injury, diffuse thyroid enlargement, and hypothyroidism. In large doses it may reduce the production of erythrocytes.

References.

1. Kennedy A, *et al.* Fatal myocardial disease associated with industrial exposure to cobalt. *Lancet* 1981; i: 412–4.
2. Cugell DW, *et al.* The respiratory effects of cobalt. *Arch Intern Med* 1990; 150: 177–83.
3. Evans P, *et al.* Cobalt and cobalt compounds. *Toxicity Review 39*. London: HMSO,1993.
4. Torresani C, *et al.* Erosive oral lichen planus due to sensitization to cobalt chloride. *Clin Exp Dermatol* 1994; 19: 535–6.
5. Krakowiak A, *et al.* Occupational asthma caused by cobalt chloride in a diamond polisher after cessation of occupational exposure: a case report. *Int J Occup Med Environ Health* 2005; 18: 151–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Infladase Forte.

Multi-ingredient Preparations. *Arg.*: Gingeron; Total Magnesiano Sport; *Fr.*: Stimuplexe†; *Hung.*: Ferrocomp; Humet-R; *Indon.*: Emineton; Nonemi; *Philipp.*: Ferroplex.

Homoeopathic Preparations. *Canad.*: Formula FA 224†; Formula PC 223†; Weight Loss Kit†; *Ger.*: Chirofossat; Infl-China.

Cobicistat *(USAN, rINN)*

Cobicistatum; GS-9350; Кобицистат.
(1,3-Thiazol-5-yl)methyl (5*S*,8*R*,11*R*)-8,11-dibenzyl-2-methyl-5-[2-(morpholin-4-yl)ethyl]-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-3,6-dioxo-2,4,7,12-tetraazatridecan-13-oate.
$C_{40}H_{53}N_7O_5S_2$=776.0
CAS — 1004316-88-4.
ATC — V03AX03.
ATC Vet — QV03AX03.
UNII — LW2E03M5PG.

Profile

Cobicistat is a pharmacokinetic enhancer used similarly to low-dose ritonavir (p. 1013.1) to boost the concentrations of antiretrovirals; it has no antiretroviral activity itself. Cobicistat (150 mg) is given as a component of a four-drug, fixed-dose combination product (*Stribild, Gilead, USA* and also referred to as the Quad pill) with elvitegravir (p. 976.2), emtricitabine (p. 976.3), and tenofovir (p. 1018.1) for the treatment of HIV infection and AIDS (p. 957.2) in antiretroviral treatment-naive patients. The recommended dose is one tablet taken orally once daily with food.

Fixed-dose antiretroviral combination products containing cobicistat and atazanavir or darunavir are also being developed.

Cobicistat is metabolised mainly by the cytochrome P450 isoenzyme CYP3A and to a lesser extent CYP2D6; it is also an inhibitor of the same isoenzymes. It is an inhibitor of P-glycoprotein, breast cancer resistanance protein (BCRP), and the organic anion transporting polypeptides (OATP1B1 and OATP1B3). Concomitant use of cobicistat with drugs that are metabolised by these isoenzymes or that are substrates for these transporters may result in increased plasma concentrations of such drugs. Drugs that induce CYP3A may decrease the plasma concentration of cobicistat, while drugs that inhibit CYP3A may increase its plasma concentration.

References.

1. von Hentig N, Haberl A. Safety of pharmacoenhancers for HIV therapy. *Expert Rev Clin Pharmacol* 2012; 5: 557–68.
2. Olin JL, *et al.* Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet for HIV-1 infection treatment. *Ann Pharmacother* 2012; 46: 1671–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Tybost.

Multi-ingredient Preparations. *Jpn*: Stribild; *UK*: Stribild; *USA*: Stribild.

Coccidioidin

Coccidioidina; Кокцидиоидин.
CAS — 12622-73-0.
UNII — ZP77O7YY70.

Profile

Coccidioidin contains antigens from the fungus *Coccidioides immitis*. It has been used as an aid to the diagnosis of coccidioidomycosis and, in conjunction with other antigens, to assess the status of cell-mediated immunity. A usual dose of 0.1 mL of a 1 in 100 dilution by intradermal (intracutaneous) injection has been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Spherulin†.

Cocculus

Cocculus Indicus; Coque du Levant; Fischkörner; Fish Berry; Indian Berry; Kokkelskörner; Levant Nut; Oriental Berry; Poison-berry.
UNII — 8H0258W28U.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Anamirta Cocculus for Homoeopathic Preparations). The dried, ripe fruit of *Anamirta paniculata*. It contains not less than 0.80% of picrotoxinin, ($C_{15}H_{16}O_6$=292.3), calculated with reference to the dried drug.

Profile

Cocculus, the dried fruit of *Anamirta cocculus* (*A. paniculata*; *Menispermum cocculus*) (Menispermaceae) has been used in herbal medicines for nervous system disorders and topically as a parasiticide, but is highly toxic and has been generally superseded. The main active constituent is picrotoxin, a CNS and respiratory stimulant.

Traditionally, the berries have been used as a fish poison.

Homoeopathy

Cocculus has been used in homoeopathic medicines under the following names: Anamirta cocculus; Cocculus.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Nervatona Calm; Nervatona Focus.

Homoeopathic Preparations. *Austral.*: Nervatona Calm; Nervatona Focus; Travellers Relief; *Austria*: Nausyn; Travelex; Vertigoheel; Vertigopas; *Canad.*: Cocculine; Hylands Motion Sickness; Hylands PMS; Hylaprin; Kids Calm; Nixotinex; Travel Sickness; *Chile*: Bioactiv V; *Cz.*: Cocculine; Vertigoheel; Vita C-R15 forte†; Vita C-R15†; *Fr.*: Apomorphinum Complexe No 97†; Cocculine; Cocculus Complexe No 73; Dolitravel†; Homeogene 21†; Nausetum; Oenanthe Crocata Complexe No 78; Tabacum Compose; Tarentula Complexe No 71; *Ger.*: Calmvalera; Cerebral-Do; Cocculus Oligoplex; Curare comp; Femi-cyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Homvio-Em; Infi-China; Naranofem†; Nervoregin H; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pascolibrin; Passiflora Complex†; Procordal vertigo; Schwoneural N; Vertigo Hevert SL; Vertigo-Hevert; Vertigo-Hevert; Vertigoheel; Vertigopas; Viscum album H†; Viscum Album HM†; Zerosorin SN†; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Hung.*: Cocculine; Vertigoheel; *Neth.*: Cerebrum comp; Co-Hypert; Cocculine; Coconium-Gastreu; Gravifem†; Travelin; Vertigoheel; *Port.*: Cocculine; *Rus.*: Aurum Plus (Аурум-Плюс); Avia-Mor (Авиа-Морс); Cocculine (Коккулин); *S.Afr.*: Vertigoheel; *Switz.*: Cocculine; Nelsons Travella†; Vertigoheel; *UK*: Nausyn; Travella; *USA*: Vertigoheel.

Cocoyl Caprylocaprate

Coco-Caprylate/Caprate; Cocoylcaprylocaprat; Cocoyle, caprylocaprate de; Cocoylis Caprylocapras; Cocoylis Octanodecanoas; Kokoilo kaprilokapratas; Kokoyl oktanodekanoát; Kokoyllkaprylokaprat; Kokeyyllkaprylokapraatti; Kókuszalkoholok kaprilátjai és kaprátjai; Коко-каприлат/капрат.
CAS — 95912-86-0.
UNII — 8D9H4QU99H.

NOTE. The name Cetiol LC has been used as a trade mark for cocyl caprylocaprate.

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

Ph. Eur. 8: (Cocoyl Caprylocaprate). A mixture of esters of saturated C_{12} to C_{18} alcohols with caprylic (octanoic) and capric (decanoic) acids obtained by the reaction of these acids with vegetable saturated fatty alcohols. Relative density about 0.86. Viscosity about 11 mPa s. A slightly yellowish liquid. Practically insoluble in water; miscible with alcohol and with liquid paraffin.

Profile

Cocoyl caprylocaprate is used as an emollient.

Coenzyme A

CoA; CoASH; Coenzima A; Коферментт А.
5′-O-[3-Hydroxy-3-[2-(2-mercaptoethylcarbamoyl)ethylcarbamoyl]-2,2-dimethylpropyl]adenosine-3′,5′-dihydrogenphosphate 5′-trihydrogendiphosphate.
$C_{21}H_{36}N_7O_{16}P_3S$=767.5
CAS — 85-61-0.
UNII — SAA04E81UX.

Profile

Formed from adenosine triphosphate, cysteine, and pantothenic acid, coenzyme A is involved in the body in many physiological roles, including the formation of citrate, the oxidation of pyruvate, the oxidation and synthesis of fatty acids, the synthesis of triglycerides, cholesterol, and phospholipids, and the acetylation of amines, choline, and glucosamine. It has been given by injection in a variety of metabolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Redumax; *Philipp.*: Enervon-C; *S.Afr.*: Zeel; Zeel.

Homoeopathic Preparations. *Cz.*: Zeel Salbe†; *Hung.*: Zeel; *Rus.*: Zeel T (Цель Т).

Cogalactoisomerase Sodium

Cogalactoisomerasa sódica; UDPG; Uridine-5′-diphosphoglucose Sodium; Уридиндифосфатглюкоза Натрий.
$C_{15}H_{22}N_2Na_2O_{17}P_2,3H_2O$=664.3
CAS — 133-89-1 (cogalactoisomerase).

Profile

Cogalactoisomerase sodium has been used in various hepatic disorders.

Colforsin *(rINN)*

Boforsin; Colforsina; Colforsine; Colforsinum; Forscolin; Forskolin; HL-362; L-75-1362B; Колфорсин.
(3*R*,4a*R*,5*S*,6*S*,6a*S*,10*S*,10a*R*,10b*S*)-Dodecahydro-5,6,10,10b-tetrahydroxy-3,4a,7,7,10a-pentamethyl-3-vinyl-1*H*-naphtho[2,1-*b*]pyran-1-one, 5-acetate.
$C_{22}H_{34}O_7$=410.5
CAS — 66575-29-9.
UNII — 1F7A44V6OU.

Colforsin Daropate Hydrochloride *(rINNM)*

Colforsin Dapropate Hydrochloride; Colforsine, Chlorhydrate de Daropate de; Colforsini Daropatis Hydrochloridum; Hidrocloruro del daropato de colforsina; Milaforsin Hydrochloride; NKH-477; Колфорсина Даропата Гидрохлорид.
$C_{27}H_{43}NO_8$,HCl=546.1
CAS — 138605-00-2.

Profile

Colforsin is an adenylate cyclase stimulator derived from the plant *Plectranthus barbatus* (*Coleus forskohlii*) (Labiatae). It has been investigated for several conditions, including glaucoma and impotence. It is reported to have positive inotropic and bronchodilator effects. It has been used in the form of colforsin daropate hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Adehl.

Collagen

ARG-201 (type 1 bovine collagen); Colágeno; Коллаген.
ATC — B02BC07; G04BX11.
ATC Vet — QB02BC07; QG04BX11.

Pharmacopoeias. *US* includes Bovine Acellular Dermal Matrix and Scaffold Human Dermis.

USP 36: (Bovine Acellular Dermal Matrix). A remodelable collagen scaffold derived from fetal or neonatal bovine skin. It is presented as a flat white sheet that is cut to size and hydrated in sterile saline solution before implantation. It is utilised as a structural scaffold in orthopaedic, neurosurgical, urogynaecological, dermatological, plastic, and other reconstructive procedures. The source fetal or neonatal bovine skin is mechanically and chemically processed to isolate the dermis and remove cells and cellular components. To prevent the transmission of infectious disease, the manufacturing process is validated to inactivate viruses potentially present in the source material. To prevent the spread of transmissible spongiform encephalopathies, the source material is acquired from appropriate geographic locations. Store at 15 degrees to 30 degrees.

USP 36: (Scaffold Human Dermis). It is derived from donated allograft human dermis that is processed to remove cells and freeze-dried to remove moisture while preserving biologic components and structure of the dermal matrix. It is biocompatible and supports remodeling by the recipient's own tissue. The matrix is composed of native human dermal architecture, consisting of collagen (mainly collagen type I, with additional components of collagen types III and IV), chondroitin sulfate and hyaluronic acid glycosaminoglycans, and elastin. The product can be provided in a sheet or powder form. The donated human skin is processed in a manner that removes all cellular components, including the epidermal layer and dermal cells. The resulting product is then rendered into a particulate form (microsized), with a mean particle size of less than 100 micrometres, by processing with a freezer mill. Scaffold Human Dermis does not contain intact cells, cell nuclei, or chemically induced crosslinks. Human skin used to produce Scaffold Human Dermis is obtained from sources that have passed applicable donor eligibility requirements for relevant communicable diseases.

Profile

Collagen is a fibrous protein component of mammalian connective tissue making up almost one third of the total body protein.

Collagen, processed in a variety of ways, has been used in surgery as a haemostatic and as a repair and suture material. For cosmetic purposes it has been injected into the dermis to correct scars and other contour deformities of the skin. Collagen implants have been used to block tear outflow in the management of dry eye (p. 2190.1).

Intraurethral administration of collagen has been used in the treatment of stress incontinence (p. 2349.2). There has also been interest in the use of oral collagen to suppress the inflammatory process in rheumatoid arthritis (p. 13.2), osteoarthritis (p. 12.3), and scleroderma (p. 1938.3).

Elastin, another component of connective tissue, is an ingredient, often with collagen, of various topical preparations promoted for skin disorders.

References.

1. Herschorn S, *et al.* Early experience with intraurethral collagen injections for urinary incontinence. *J Urol (Baltimore)* 1992; **148**: 1797–1800.
2. Sieper J, *et al.* Oral type II collagen treatment in early rheumatoid arthritis: a double-blind, placebo-controlled, randomized trial. *Arthritis Rheum* 1996; **39**: 41–51.
3. Stanton SL, Monga AK. Incontinence in elderly women: is periurethral collagen an advance? *Br J Obstet Gynaecol* 1997; **104**: 154–7.
4. Anonymous. GAX collagen for genuine stress incontinence. *Drug Ther Bull* 1997; **35**: 86–7.
5. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum* 2000; **30**: 87–99.
6. Hamraoui K, *et al.* Efficacy and safety of percutaneous treatment of iatrogenic femoral artery pseudoaneurysm by biodegradable collagen injection. *J Am Coll Cardiol* 2002; **39**: 1297–1304.
7. Corcos J, *et al.* Multicenter randomized clinical trial comparing surgery and collagen injections for treatment of female stress urinary incontinence. *Urology* 2005; **65**: 898–904.
8. Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. *Curr Med Res Opin* 2006; **22**: 2221–32.
9. Poon CI, Zimmern PE. Is there a role for periurethral collagen injection in the management of urodynamically proven mixed urinary incontinence? *Urology* 2006; **67**: 725–9.
10. Sakamoto K, *et al.* Long-term subjective continence status and use of alternative treatments by women with stress urinary incontinence after collagen injection therapy. *World J Urol* 2007; **25**: 431–3.
11. Postlethwaite AE, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of oral type I collagen treatment in patients with diffuse cutaneous systemic sclerosis: I. oral type I collagen does not improve skin in all patients, but may improve skin in late-phase disease. *Arthritis Rheum* 2008; **58**: 1810–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Covadenyl; Eurohair; Hidroplus CL; Medic-S; Membracel; Skinderm CL; *Austral.*: Ionil Rinse†; Zyderm†; Zyplast†; *Chile*: Artrimax; Cosmoplast†; *Ger.*: Catrix†; Collosa†; Hemocol; Medifome†; TissuCone; TissuFleece; TissuFoil; *Gr.*: Colgen; Gelfix; *India*: Collafex; Gelfix; *Ital.*: Condress; Idroskin; Suprasorb C; *Malaysia*: Bio Coll; *Mex.*: Fibroquel; *NZ*: Contigen; Zyderm; Zyplast; *Singapore*: CosmoDerm; CosmoPlast; Terraflex; *UK*: Contigen; *USA*: Avitene†.

Multi-ingredient Preparations. *Arg.*: Amenite B; Amenite Plus; Aristaloe; Colageno + C; Collagen T2-Gag; Dayflex C; E-Devit; Estri-Atlas; Fibracol Plus; Galenic Restaurador Capilar; Hairplus; Hidrosam T; Hidrosam; HSN; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Medicreme; Piroctol; Pityrum; Puraloe Nutritiva; Rep-Cartil; Rominafort; Skinderm R; Totalos Plus; Turgent Colageno; Ukase Lulitis; Zinc-S Plus; *Belg.*: Duracoll; *Chile*: Acnoxyl Gel Humectante; Estri-Atlas; *Fr.*: Flex-Tonic; Lubri-Mucal; Osteocalm; Taido; *Ger.*: Collapat II; Septocoll; Targobone†; *Hong Kong*: TachoComb; *Indon.*: Biolastin; Colaskin; Jointfit; Legreskin; OA Plus; *Ital.*: Artrodue; Biomineral 5-Alfa Shampoo; Emofix; Osteoclar; Promogran Prisma; Promogran; Reumilase Plus; Reumilase SD; Reumilase; Secril; Unidermo; Vitreoclar Crono; *Malaysia*: Balance Elastin B; Evelle; *Philipp.*: Gloww; *Rus.*: Combutec-2 (Комбутек-2); Methuracol (Метураколл); TachoComb (ТахоКомб); *Singapore*: Articolase (w/glucosamine); BCC; Evelle; Glow; RejuvaSkin Anti-Aging Serum; Seven Seas JointCare Max; TachoComb; *Switz.*: Gorgonium; *UK*: Collatamp EG; Jointace; JointCare Max; *Ukr.*: TachoComb (Тахокомб); *USA*: PDP Liquid Protein; *Venez.*: Artrosamin.

Collagenase ⊗

Clostridiopeptidas; Clostridiopeptidasa A; Clostridiopeptidase A; Clostridiopeptidasum A; Colagenasa; EC 3.4.24.3; Klostridiopeptidaasi A; Коллагеназа.

CAS — 9001-12-1.

ATC — D03BA02.

ATC Vet — QD03BA02.

UNII — 9X7O8V25IT (collagenease Clostridium histolyticum *gene colh isoenzyme aux-II); 231982L46K (collagenease* Clostridium histolyticum *gene colg isoenzyme aux-I); 15Z7208B52 (collagenase* Clostridium histolyticum*).*

Units

Collagenase potency is expressed in units based on the amount of enzyme required to degrade a standard preparation of undenatured collagen.

Uses and Administration

Collagenase is a proteolytic enzyme derived from the fermentation of *Clostridium histolyticum* and has the ability to break down collagen. Preparations containing collagenase are used topically for the debridement of dermal ulcers and burns, and possibly other necrotic lesions, to facilitate granulation and epithelialisation. Collagenase is given by intralesional injection in the treatment of Dupuytren's contracture. It is injected in a dose of 580 micrograms into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint. The injection may be given up to 3 times per cord at intervals of 4 weeks if the contracture remains. Only one cord may be injected at a time; if patients have multiple contractures with palpable cords, each cord should be treated in a sequential order. Collagenase has also been given by injection into the intervertebral disc for chemonucleolysis in the treatment of lumbar disc herniation (see Low Back Pain, p. 9.2). Collagenase is under investigation for use in Peyronie's disease and frozen shoulder.

Chemonucleolysis. Collagenase has been studied as an alternative to chymopapain (p. 2477.1) for chemonucleolysis because of the risk of anaphylaxis with the latter. Although early studies with collagenase reported benefit, there were also reports of back pain and muscle spasm.[1] Collagenase was not as effective as chymopapain in a comparative study,[2] and further study may be warranted before a firm recommendation can be made.

1. Brown MD. Update on chemonucleolysis. *Spine* 1996; 21 (24 suppl): 62S–68S.
2. Wittenberg RH, *et al.* Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study. *Spine* 2001; 26: 1835–41.

Dupuytren's disease. Collagenase has been reported to be of benefit in the treatment of Dupuytren's contracture.[1,2]

1. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg (Am)* 2007; 32: 767–74.
2. Hurst LC, *et al.* Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009; 361: 968–79.

Peyronie's disease. Beneficial effects have been reported with intralesional collagenase in men with Peyronie's disease.[1-3]

1. Gelbard MK, *et al.* The use of collagenase in the treatment of Peyronie's disease. *J Urol (Baltimore)* 1985; 134: 280–3.
2. Gelbard MK, *et al.* Collagenase versus placebo in the treament of Peyronie's disease: a double-blind study. *J Urol (Baltimore)* 1993; 149: 56–8.
3. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med* 2008; 5: 180–7.

Adverse Effects and Precautions

Hypersensitivity reactions to collagenase may occur.

Local burning, erythema, and pain have been reported at the site of application when used topically. It has been suggested that debridement of infected wounds may increase the risk of bacteraemia and that patients should be watched for signs of systemic bacterial infection. The activity of collagenase may be reduced by antiseptics containing detergents, hexachlorophene, and heavy metal ions.

Injection of collagenase into tendons, nerves, blood vessels, or other collagen-containing structures in the hand should be avoided because of the risk of permanent injury such as tendon rupture or damage to ligaments. Collagenase injections should be used with caution in patients with coagulation disorders or in those who have received anticoagulants (excluding low-dose aspirin) within 7 days before the injection because of the risk of ecchymosis, bruising or injection-site haemorrhage.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Xiapex; *Belg.*: Iruxol Mono; Xiapex; *Braz.*: Iruxol Mono; Kollagenase; *Canad.*: Santyl; *Cz.*: Xiapex; *Denm.*: Xiapex; *Fin.*: Xiapex; *Fr.*: Xiapex; *Ger.*: Xiapex; *Gr.*: Iruxol Mono; Xiapex; *Hong Kong*: Iruxol Mono†; *Hung.*: Xiapex; *Irl.*: Xiapex; *Ital.*: Noruxol; Xiapex; *Neth.*: Novuxol; Xiapex; *Norw.*: Xiapex; *Pol.*: Xiapex; *Port.*: Ulcerase; Xiapex; *Rus.*: Kollalysin (Коллализин); *Spain*: Xiapex; *Swed.*: Xiapex; *Switz.*: Iruxol Mono; Xiapex; *Turk.*: Novuxol; *UK*: Xiapex; *USA*: Santyl; Xiaflex; *Venez.*: Iruxol.

Multi-ingredient Preparations. *Arg.*: Iruxol; *Braz.*: Gino Kollagenase; Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; *Cz.*: Iruxol Mono; *Fin.*: Iruxol Mono; Iruxol†; *Hung.*: Iruxol Mono†; *Indon.*: Plasmin; *Irl.*: Iruxol Mono; *Ital.*: Iruxol; *Malaysia*: Iruxol Mono; *Mex.*: Ulcoderma†; *Philipp.*: Plasmin; *Rus.*: Iruxol (Ируксол)†; *S.Afr.*: Iruxol Mono; *Spain*: Iruxol Mono; Iruxol Neo.

Colophony

Colofonia; Coloph.; Colophane; Colophonium; Kalafuna; Kanifolija; Kolofoni; Kolofónium; Kolofonium; Kolophonium; Resin; Resina Pini; Resina Terebinthinae; Rosin; Канифоль.

UNII — 88S87KL877.

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

Ph. Eur. 8: (Colophony). The residue remaining after distillation of the volatile oil from the oleoresin obtained from various species of *Pinus*. Translucent, pale yellow to brownish-yellow, angular, irregularly shaped, brittle, glassy pieces of different sizes the surfaces of which bear conchoidal markings. Do not reduce to a fine powder.

Profile

Colophony is an ingredient of some collodions and plastermasses. It has been used as an ingredient of ointments and dressings for wounds and minor skin disorders. Skin sensitisation and allergic respiratory symptoms have been reported.

Hypersensitivity. Reviews.

1. Downs AM, Sansom JB. Colophony allergy: a review. *Contact Dermatitis* 1999; 41: 305–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Biopin (Биопин).

Multi-ingredient Preparations. *Arg.*: Adhesol; *Austria*: Ehrenhofer-Salbe; Vulpuran; *Gr.*: Ilon; *Ital.*: Fialetta Odontalgica Dr Knapp; *Mex.*: Parche Negro Belladona; *UK*: Dispello; Herbheal Ointment; Pickles Corn Caps.

Pharmacopoeial Preparations

BP 2014: Flexible Collodion.

Comfrey

Boneset; Comfrey Root; Common Comfrey; Consolidae Radix; Consuelda; Sinfito mayor; Symphytum; Окопник лекарственный.

ATC Herb — HM02AX5004 (Symphytum officinale: root); HA02WX5003 (Symphytum officinale: herb); HA02WB5001 (Symphytum officinale: root); HD03WC5002 (Symphytum officinale: root); HD03WC5001 (Symphytum officinale: herb).

UNII — D05HXK6R3G (comfrey); DG4F8T839X (comfrey leaf); M9VVZ08EKQ (comfrey root).

NOTE. Boneset is also a common name used for *Eupatorium perfoliatum* (see p. 2459.1). Purple boneset is Gravel Root, p. 2522.1.

Pharmacopoeias. *Br.* includes Symphytum Officinale Root for Homoeopathic Preparations and Symphytum Officinale Root, Ethanol. decoctum for Homoeopathic Preparations.

BP 2014: (Symphytum Officinale Root for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

BP 2014: (Symphytum Officinale Root, Ethanol Decoction for Homoeopathic Preparations). The fresh root of *Symphytum officinale*.

Uses and Administration

Comfrey consists of the dried root and rhizome of *Symphytum officinale* (Boraginaceae); the leaf has also been used. It contains about 0.7% of allantoin, large quantities of mucilage, and some tannin. It may also contain pyrrolizidine alkaloids.

Comfrey was formerly used as an application to wounds and ulcers to stimulate healing and was also given systemically for gastric ulceration. It has been applied topically in the treatment of inflammatory disorders. The healing action of comfrey has been attributed to the presence of allantoin (p. 1693.1).

Oral preparations of comfrey have been withdrawn or banned in some countries because of toxicity—see below.

Homoeopathy

Comfrey has been used in homoeopathic medicines under the following names: Symphytum officinale; Symph. of.; Symphytum.

References.

1. Stickel F, Seitz HK. The efficacy and safety of comfrey. *Public Health Nutr* 2000; 3: 501–8.
2. Grube B, *et al.* Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine* 2007; 14: 2–10.
3. D'Anchise R, *et al.* Comfrey extract ointment in comparison to diclofenac gel in the treatment of acute unilateral ankle sprains (distortions). *Arzneimittelforschung* 2007; 57: 712–16.

Adverse Effects

Ingestion of comfrey has been associated with hepatotoxicity.

Effects on the liver. Toxic pyrrolizidine alkaloids have been isolated from several species of comfrey plants including common comfrey (*Symphytum officinale*), prickly comfrey (*S. asperum*), and Russian comfrey (*S. uplandicum*). Ingestion of plants containing pyrrolizidine alkaloids is a common cause of hepatic veno-occlusive disease in developing countries[1] and pyrrolizidine alkaloid hepatotoxicity presumably due to comfrey has been reported in North America and Europe.[1,2] Pulmonary endothelial hyperplasia and carcinogenic activity have also been reported in *animals*.[1,2]

1. Ridker PM, McDermott WV. Comfrey herb tea and hepatic veno-occlusive disease. *Lancet* 1989; i: 657–8.
2. Bach N, *et al.* Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med* 1989; 87: 97–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Flexagil; *Austria*: Traumaplant; *Belg.*: Flexagile; *Chile*: Traumaplant; *Cz.*: Traumaplant; *Fr.*: Epidermine†; *Ger.*: Kytta-Plasma f; Kytta-Salbe f; Traumaplant; *Hung.*: Flexagil; *Indon.*: Mediflor†; *Israel*: Traumaplant; *Ital.*: Kytta; *Port.*: Elas; *Switz.*: Kytta Pommade; Symphosan†; Traumaplant; *UK*: Comfrelieve; *Venez.*: Traumaplant.

Multi-ingredient Preparations. *Arg.*: Lavandula Oligoplex; *Austral.*: Joint & Muscle Cream; *Canad.*: Natraway Sport I & 2†; Natraway Sport 3†; *Fr.*: Cicactive; Tigre de Chine; *Ger.*: Kytta-Balsam f; Rhus-Rheuma-Gel N; *Israel*: Comfrey Plus; *S.Afr.*: Zeel; Zeel; *Switz.*: DUL-X Cool; Gel de consoude†; Impuls a la consoude; Keppur; Keppur; Kytta Baume†; Perskindol Cool Consoude; *Turk.*: Symphosan; *Ukr.*: Perfectil Plus (Перфектил Плюс).

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Sports Ice Joint & Muscle; *Austria*: Osteoplex; Repisan; Steiroplex; Traumeel; Wirbelsaule- und Gelenkstropfen Nr 2†; *Canad.*: Arnica + Pain Relief; Calendula Ointment†; Capsicum + Arthri-Cream; Traumeel; *Chile*: Osteofix; *Cz.*: Traumeel; Zeel Salbe†; *Fr.*: Symphytum Complexe No 48†; *Ger.*: Araniforce rheuma†; Arnica/Symphytum comp; Chirofossat; Infi-Symphytum; Infihepan; Inflossan; Odonton-Echtroplex; Osteoplex; Ruta-Gastreu N R55; Steirocall; Steiroplex†; Symphytum Rowo†; Traumeel S; *Hung.*: Traumeel; Zeel; *Neth.*: Arnilite; Homeocare Exercito; Kruidvat Homeopathie Spier- en gewrichtsgel†; Spiroflor; Traumeel H; Traumeel S; *Rus.*: Repisan (Реписан); Rewma-Gel (Ревма-Гель); Traumeel S (Траумель С); Zeel T (Цель Т); *S. Afr.*: Traumeel S; *Switz.*: Contusin; Nelsons Traumatica†; Omida Gel Antirhumatismal; Regenaplex Nr. 88b; Traumeel; *Ukr.*: Reuma-Gel (Ревма-Гель); Traumeel S (Траумель С); *USA*: Traumeel; *Venez.*: Traumeel.

Complement Blockers

Inhibidores del complemento; Блокаторы Комплемента.

Profile

Complement is a group of plasma and cellular proteins contributing to the innate immune system and is so called because it complements the microbicidal action of antibodies. The complement system is activated by the antigen-antibody complex followed by a cascade reaction of complement proteins culminating in microbial cell lysis. Complement also plays a part in many other physiological processes and regulatory mechanisms are in place to prevent inflammatory damage to host tissues through the inappropriate activation of complement. Hereditary or acquired abnormalities of the complement system are associated with a variety of disorders depending on which part of the system is affected, and include recurrent infections, partial lipodystrophy, hereditary angioedema, paroxysmal nocturnal haemoglobinuria, non-specific vasculitis, glomerulonephritis, cardiovascular disease, rheumatoid arthritis, sepsis, asthma, acute respiratory distress syndrome, psoriasis, SLE, bullous pemphigoid, discoid lupus, and graft survival after solid organ transplantation.

Several substances are used or are under investigation for their ability to block activation of the complement system:

- complement C1 esterase inhibitor (below) is given as replacement therapy in the treatment of hereditary angioedema
- eculizumab (p. 2499.1) is a monoclonal antibody that targets the terminal C5 protein of complement and is given in the treatment of paroxysmal nocturnal haemoglobinuria
- pexelizumab (p. 2587.2) is a similar substance under investigation in patients undergoing coronary artery revascularisation procedures
- mirococept (APT-070, SCR1-3) is a derivative of soluble complement receptor type 1 (SCR1) under investigation for the prevention of post transplantation graft dysfunction
- TP-10, a form of SCR1 has also been investigated for respiratory disorders
- myristoylated-peptidyl-recombinant human CD59 is under investigation for paroxysmal nocturnal haemoglobinuria

References.

1. Bhole D, Stahl GL. Therapeutic potential of targeting the complement cascade in critical care medicine. *Crit Care Med* 2003; 31 (suppl): S97–S104.
2. Brook E, *et al.* Opportunities for new therapies based on the natural regulators of complement activation. *Ann N Y Acad Sci* 2005; 1056: 176–86.

Complement C1 Esterase Inhibitor

Factor de inhibición de la C1 esterasa; Inhibidor de la C1 esterasa; C1-Ингибитор Комплемента.

ATC — B06AC01.
ATC Vet — QB06AC01.
UNII — 6KIC4BB60G.

Conestat Alfa *(rINN)*

Conestatum alfa; rhC1INH; Конестат Альфа.

Human plasma protease C1 inhibitor (C1 esterase inhibitor) (*N,O*-glycosylated recombinant protein expressed in the mammary gland of transgenic rabbits), glycoform α.

CAS — 80295-38-1.
ATC — B06AC04.
ATC Vet — QB06AC04.
UNII — 5QS67N4551.

NOTE. The name Rhucin has been used as a trade mark for conestat alfa.

Uses and Administration

Complement C1 esterase inhibitor is an endogenous complement blocker (above) that plays a role in regulation of the complement system. It is prepared from human plasma and given as replacement therapy in hereditary angioedema (below), in which there is a deficiency of natural complement C1-esterase inhibitor. In the treatment of an acute attack, or for prophylaxis before surgical procedures, a dose of 20 units/kg is given by slow intravenous injection or infusion. Further doses may be necessary, according to patient response. For routine prophylaxis, a dose of 1000 units may be given once every 3 or 4 days. For doses used in children, see below.

Conestat alfa is recombinant human complement C1 esterase inhibitor used in the treatment of acute attacks in patients with hereditary angioedema. It is given by intravenous injection over about 5 minutes in a dose of 50 units/kg in patients weighing up to 84 kg, or for patients of 84 kg and over, in a dose of 4200 units. In most cases, one dose should be sufficient to arrest the attack but if required, a second dose of 50 units/kg up to a maximum of 4200 units may be given. No more than 2 doses should be given in 24 hours. Conestat alfa is also under investigation in the treatment of capillary leak syndrome, for the prevention of delayed graft function in organ transplantation, and as a means of limiting reperfusion injury in patients with acute myocardial infarction (below).

Administration in children. Complement C1 esterase inhibitor may be used in neonates, infants, and children for the treatment of acute attacks of hereditary angioedema, or as prophylaxis before surgical procedures. A dose of 20 units/kg is given by slow intravenous injection or infusion, and may be repeated according to patient response.

Hereditary angioedema. Hereditary angioedema, formerly known as hereditary angioneurotic oedema, is a rare autosomal dominant disease caused by either a deficiency of complement C1 esterase inhibitor or, more rarely, a lack of functioning inhibitor.[1-6] The disease presents as episodic attacks of oedema, usually of the extremities and face, and often involving the gastrointestinal mucosa producing abdominal pain. A non-pruritic rash may also occur. A few patients develop life-threatening laryngeal oedema. Attacks generally last about 1 to 3 days and may occur as frequently as weekly or there may be years between attacks. The first attack may occur at any age although initial presentation in childhood is most common. Trauma, especially dental surgery, illness, and emotional stress may provoke an attack although often there is no precipitating factor. Some medications such as ACE inhibitors or oestrogens found in hormonal contraceptives or HRT can act as triggers.

Treatment of the acute attack is essentially supportive. If laryngeal oedema is present adrenaline may be given (as for Anaphylaxis, p. 1293.2) even though patients with hereditary angioedema often fail to respond adequately; antihistamines and corticosteroids are generally considered to be ineffective. The mainstay of treatment of an acute attack is replacement therapy with complement C1 esterase inhibitor.[1-3] A recombinant form, conestat alfa, is also available.[6] Fresh frozen plasma has been used although there is a risk of initially exacerbating the oedema due to the presence of other complements in the plasma. Tracheostomy or tracheal intubation may be necessary. If complement C1 esterase inhibitor is not available, androgens or antifibrinolytics may be tried in higher doses than normally used for prophylaxis.[1,4] However, these generally have limited efficacy and are slow to act. More recently, ecallantide (an inhibitor of human plasma kallikrein) and icatibant acetate (a selective bradykinin B_2 antagonist) have become available for the treatment of acute attacks.[6]

Once the acute attack has subsided most patients will not require further treatment, but those who have life-threatening attacks, repeated episodes of swelling around the face or neck, or incapacitating attacks require long-term **prophylactic therapy**. A synthetic androgen (danazol or stanozolol) or an antifibrinolytic (aminocaproic acid or tranexamic acid) is effective for long-term prophylaxis.[1,2,4,5] Danazol and stanozolol raise serum concentrations of C1 esterase inhibitor possibly by enhancing its synthesis in the liver.[2] Aminocaproic acid and tranexamic acid may act by inhibiting plasmin activation.[7] A synthetic androgen is often preferred because these seem to be more effective than antifibrinolytics. In children, however, androgens are generally avoided because of their adverse effects. Nevertheless, they may be used in children, with close monitoring, when antifibrinolytics have been ineffective.[3] In some cases, long-term prophylaxis with once or twice weekly C1 esterase inhibitor may be indicated for adults when antifibrinolytics and androgens are ineffective, not tolerated, or contra-indicated.[2,4,6]

Short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental work.[2-5] Complement C1 esterase inhibitor is usually given 1 hour before the procedure, or fresh frozen plasma may be used if this is not available. Alternatively, a synthetic androgen or antifibrinolytic may be used, but these must be started several days before the procedure and continued for 2 days after.

1. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; 114: 10–16.
2. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139: 379–94. Correction. *ibid.*; 141: 189–90. [dose]
3. Farkas 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)
4. 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.
5. Zuraw BL. Hereditary angioedema. *N Engl J Med* 2008; 359: 1027–36.
6. Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs* 2008; 68: 2561–73.
7. Ritchie BC. Protease inhibitors in the treatment of hereditary angioedema. *Transfus Apheresis Sci* 2003; 29: 259–67.

Myocardial infarction. Complement C1 esterase inhibitor is being studied as a means of limiting reperfusion injury in patients with acute myocardial infarction.[1-3]

1. de Zwaan C, *et al.* Continuous 48-h C1-inhibitor treatment, following reperfusion therapy, in patients with acute myocardial infarction. *Eur Heart J* 2002; 23: 1670–7.
2. Thielmann M, *et al.* Administration of C1-esterase inhibitor during emergency coronary artery bypass surgery in acute ST-elevation myocardial infarction. *Eur J Cardiothorac Surg* 2006; 30: 285–93.
3. Patzouch K, *et al.* Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: a randomised double-blind study. *Eur J Cardiothorac Surg* 2007; 32: 326–32.

Adverse Effects and Precautions

There have been rare reports of hypersensitivity reactions, including urticaria, wheezing, and anaphylaxis, in patients given complement C1 esterase inhibitor, including conestat alfa Headache, chills, fever, and injection site reactions including redness and pain have also occurred. Thrombosis was reported in studies using doses of complement C1 esterase inhibitor higher than those licensed for hereditary angioedema.

As for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

Conestat alfa is derived from the milk of transgenic rabbits and patients should be tested for the presence of IgE antibodies against rabbit allergens. Treatment may only be started if the results are negative, and the test should be repeated once each year during treatment, or after 10 treatments, whichever occurs first.

Pharmacokinetics

In patients with hereditary angioedema, the half-life reported after intravenous injection of complement C1 esterase inhibitor during an attack-free period ranges from about 20 to 60 hours, depending on the preparation. It is slightly shorter in children and in patients with severe attacks.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Berinert P; *Austral.*: Berinert; *Austria*: Berinert; *Belg.*: Berinert; *Canad.*: Berinert; *Cz.*: Berinert; Ruconest; *Denm.*: Berinert; Cinryze; Ruconest; *Fin.*: Berinert; Cebitor; *Fr.*: Berinert; Ruconest; *Ger.*: Berinert; Cinryze; Ruconest; *Gr.*: Berinert; *Hung.*: Berinert P; *Irl.*: Cinryze; Ruconest; *Israel*: Berinert; *Neth.*: Berinert; Cetor; Cinryze; Ruconest; *Norw.*: Berinert; Cinryze; Ruconest; *Pol.*: Ruconest; *Port.*: Berinert; Ruconest; *Spain*: Berinert; Cinryze; *Swed.*: Berinert; Ruconest; *Switz.*: Berinert; *Turk.*: Cetor; *UK*: Berinert; Cinryze; Ruconest; *USA*: Berinert; Cinryze.

Condurango

Condurango Bark; Condurango cortex; Condurango, écorce de; Eagle-vine Bark; Кондуранго.

ATC Herb — HA09WA5017 (Marsdenia cundurango: *bark*).
UNII — R23QIR6YBA.

Pharmacopoeias. In *Jpn* and *Swiss*.

Profile

Condurango, the dried stem bark of *Marsdenia condurango* (*Gonolobus condurango*) (Asclepiadaceae), has been used as a bitter.

Homoeopathy

Condurango has been used in homoeopathic medicines under the following names: Marsdenia cundurango; Cond.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Sigman-Haustropfen; *Braz.*: Camomila; *Ger.*: Pascopankreat; *Hung.*: Kilo-Nit; *Pol.*: Herbaton†; *Switz.*: Kernosan 26; Padma-Lax; Padmed Laxan; Stomacine.

Homoeopathic Preparations. *Austria*: Lymphdiaral; *Fr.*: Gastro-Drainol†; Hydrastis Compose; Nux Vomica Compose; *Ger.*: Antimas†; Flenin; Hewesoor N†; Juv 110; Lowe-Komplex Nr 6; Mucosa compositum; *Neth.*: Lymphdiaral; *USA*: Preferred Remedies Antacid.

Congo Red

CI Direct Red 28; Colour Index No. 22120; Czerwień Kongo; Rojo Congo; Rubrum Congoensis; Конго Красный.

Disodium 3,3′-[biphenyl-4,4′-diylbis(azo)]bis[4-aminonaphthalene-1-sulphonate].

$C_{32}H_{22}N_6Na_2O_6S_2$=696.7

CAS — 573-58-0.
UNII — 3U05FHG59S.

Profile

Congo red is used as a stain in the diagnosis of amyloidosis. It causes amyloid in tissue samples to fluoresce under polarised light.

Conivaptan Hydrochloride *(rINN)* ⊗

CI-1025; Conivaptan, Chlorhydrate de; Conivaptán, hidrocloruro de; Conivaptani Hydrochloridum; YM-087 (conivaptan or conivaptan hydrochloride); Конивантана Гидрохлорид.

4″-[(4,5-Dihydro-2-methylimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]-2-biphenylcarboxanilide hydrochloride.

$C_{32}H_{26}N_4O_2,HCl$=535.0

CAS — 210101-16-9 (conivaptan); 168626-94-6 (conivaptan hydrochloride).

ATC — C03XA02.

ATC Vet — QC03XA02.

UNII — 75L57R6X36.

Uses and Administration

Conivaptan hydrochloride is a vasopressin V_{1a} and V_2 receptor antagonist. In the management of hyponatraemia it acts mainly at V_2 receptors in the renal collecting ducts to increase the excretion of free water. It is used to treat euvolaemic and hypervolaemic hyponatraemia (p. 1778.1). It has also been studied for heart failure, but safety has not been established and it should only be used if the benefits outweigh the risks.

Conivaptan hydrochloride is given by intravenous infusion. To minimise infusion site irritation, it should be diluted in glucose 5% infusion and given through a large vein; the infusion site should be changed every 24 hours. A loading dose of 20 mg is given over 30 minutes, followed by a continuous infusion of 20 mg over 24 hours. Treatment may be continued at a dose of 20 mg daily for 1 to 3 days titrated to a maximum of 40 mg daily if required. The maximum duration of the infusion is 4 days. If a rapid rise in serum-sodium occurs (more than 12 mmol/litre in 24 hours) conivaptan should be stopped, and serum-sodium and neurological status should be carefully monitored because of the risk of osmotic demyelination syndrome. If hypovolaemia or hypotension develop, conivaptan should be stopped and volume status and vital signs should be monitored. Conivaptan may be resumed at a lower dose, if still indicated, when the rise in serum-sodium has stopped, if there is no evidence of adverse neurological effects and the patient is euvolaemic and no longer hypotensive. For dosage reductions in hepatic and renal impairment, see below.

References.
1. Walter KA. Conivaptan: new treatment for hyponatremia. *Am J Health-Syst Pharm* 2007; 64: 1385–95.

Administration in hepatic impairment. In patients with hepatic impairment (Child-Pugh Class A, B, or C), conivaptan should be given intravenously in an initial loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to 4 days. If serum sodium does not rise at the desired rate, the dose may be titrated upwards to 20 mg over 24 hours.

Administration in renal impairment. In patients with moderate renal impairment (creatinine clearance 30 to 60 mL/min) conivaptan should be given intravenously in an initial loading dose of 10 mg followed by a continuous infusion of 10 mg over 24 hours for 2 to 4 days. If serum sodium does not rise at the desired rate, the dose may be titrated upwards to 20 mg over 24 hours. Conivaptan is not recommended in patients with severe renal impairment or anuria (see below).

Adverse Effects and Precautions

The most common adverse effects of conivaptan are infusion site reactions such as erythema, pain, phlebitis, and swelling, which are usually mild but can be severe enough in some patients that infusion must be stopped. Other adverse effects include atrial fibrillation, gastrointestinal disturbances, pyrexia, thirst, electrolyte disturbances, headache, and hypertension or hypotension.

Conivaptan is contra-indicated in hypovolaemic hyponatraemia, and is not indicated for the treatment of patients with congestive heart failure. Rapid correction of serum-sodium concentrations with conivaptan could increase the risk of osmotic demyelination syndrome. Conivaptan should be used with caution in hepatic or renal impairment because systemic exposure can be increased. It is not recommended at all in patients with severe renal impairment or those who are anuric because of unlikely benefit.

Interactions

As a substrate of the cytochrome P450 isoenzyme CYP3A4, concentrations of conivaptan can be increased by CYP3A4 inhibitors. The use of conivaptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contra-indicated. Conivaptan itself is also a potent inhibitor of CYP3A4 and may increase the concentrations of other substrates of this isoenzyme, including amlodipine, midazolam, and simvastatin.

For the effect of conivaptan on digoxin, see p. 1358.1.

Pharmacokinetics

Conivaptan is metabolised by the cytochrome P450 isoenzyme CYP3A4, but inhibits its own metabolism. Using a regimen of intravenous loading dose followed by continuous infusion, concentrations of conivaptan initially decrease from the loading dose peak over about 12 hours, then gradually increase. After stopping the infusion, conivaptan has an elimination half-life of about 5 hours. Conivaptan is highly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Vaprisol.

Convallaria

Convalaria; Convallariae Herba; Lily of the Valley; Lirio Convalio; Lirio de los Valles; Maiblume; Maiglöckchenkraut; May Lily; Muguet; Mugueta; Muguete; Ziele konwalii; Ландыш.

CAS — 3253-62-1 (convallatoxol); 13473-51-3 (convalloside); 13289-19-5 (convallatoxoloside); 508-75-8 (convallatoxin).

ATC Herb — HC01AX5002 (Convallaria majalis: *herb*).

UNII — 4R8IGU6CQ3 (Convallaria majalis); *261W7X975U* (Convallaria majalis *bulb*); *T84WVY4I0G* (Convallaria majalis *flower*); *QHH4HVF5QE* (Convallaria majalis *flowering*); *4G7VTP9FC4* (Convallaria majalis *flowering top*).

Pharmacopoeias. In *Ger.* and *Pol.* (from *C. majalis* or closely related species).

Profile

Convallaria consists of the dried flowers, herb, or the rhizomes and roots of lily of the valley, *Convallaria majalis* (Liliaceae). Several crystalline glycosides have been obtained from the plant including convallarin, convalloside, convallatoxoloside, and convallatoxin.

Convallaria contains cardiac glycosides and has actions on the heart similar to those of digoxin (p. 1353.3). Convallaria is used in herbal medicine.

Homoeopathy

Convallaria has been used in homoeopathic medicines under the following names: Convallaria majalis; Conval. m.

Convallaria majalis has been designated unsafe for inclusion in foods, beverages, or drugs by the FDA in the USA.[1]

1. Larkin T. *FDA Consumer* 1983; 17(Oct.): 5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Convafort; *Ukr.*: Corglycon (Коргликон).

Multi-ingredient Preparations. *Arg.*: Passacanthine; *Ger.*: Mirotonf†; *Mex.*: Verisan Triplex; *Pol.*: Cardiol C; Kelicardina; Neocardina; *Rus.*: Carniland (Карниланд); Valocormid (Валокормид); Zelenin (Зеленин).

Homoeopathic Preparations. *Austria*: Aurumheel; Homviocorin; Pumpan; *Canad.*: Aurumheel†; *Ger.*: Angioton H; Angioton S†; Asthmavowen-N†; Cardioject; Confludin N; Conva-cyl Ho-Len-Complex; Convallocor; Convallysan M; Convastabil; Cor Plus; Cor-loges; Goldtropfen S; HanoCor N; Homviocorin spezial; Infi-Camphora; Lowe-Komplex Nr 10; Lowe-Komplex Nr 13; Naranocor HM; Roth's Rotacard; Schworocard; Steicardin N†; *Hung.*: Aurumheel; *Rus.*: Pumpan (Пумпан); *Switz.*: Gouttes d'Or; *Ukr.*: Aurocard (Аурокард); Homviocorin-N (Хомвиокорин-N); Pumpan (Пумпан).

Copper Acetate

Cuivre, acétate de; Cupri acetas; Cupric Acetate; Kopparacetat; Kupariasetaatti; Miedzi(II) octan; Vario acetatas; Ацетат Меди; Уксуснокислая Медь.

$(C_2H_3O_2)_2Cu,H_2O$=199.6

CAS — 142-71-2 (anhydrous).

UNII — 39M11XPH03.

Pharmacopoeias. *Eur.* (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Copper Acetate Monohydrate for Homoeopathic Preparations; Cupri Acetas Monohydricus ad Praeparationes Homoeopathicas). Greenish-blue crystals or green powder. Soluble in water; slightly soluble or very slightly soluble in alcohol.

Profile

Copper acetate has been used in a variety of dermatological preparations. It is now more usually used complexed with a tripeptide in the form of prezatide copper acetate (p. 1718.1). This acts as a source of ionic copper, which is needed by lysyl oxidase, a copper-dependent enzyme that has a crucial role in the crosslinking of collagen and elastin. For the nutritional and other uses of copper and its salts, see p. 2057.2.

Homoeopathy

Copper acetate has been used in homoeopathic medicines under the following names: Cuprum aceticum; Cuprum acet; Cup. acet.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Verel; *Mex.*: Emplasto Monopolis.

Homoeopathic Preparations. *Austria*: Dalektro; Gripagil Husten und Bronchialtropfen; *Canad.*: Drosera Homaccord; Homeo-Form I†; Husteel†; Insomnia; Pertudoron 2†; Spascupreel; *Cz.*: Husteel; *Fr.*: Amanita Complexe No 75; Cina Complexe No 55†; Drosera Complexe No 64; Geranium Complexe No 108†; Lobelia Complexe No 74†; Momordica Complexe No 109†; Nervopax; Oenanthe Crocata Complexe No 78; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Zincum Cyanidum Complexe No 101†; *Ger.*: Bomapect N; Cocculus Oligoplex; Jutussin; Pertudoron 2; Presselin All; Pulmosan; Vasa-Gastreu N R63; Viropect; *Hung.*: Husteel; *Neth.*: Homeocare Nervo; Husteel; Jutussin R9; Neurovita; *Switz.*: Regenaplex Nr 12; Regenaplex Nr. 24b.

Corbadrine *(rINN)* ⊗

Corbadrina; Corbadrinum; *l*-3,4-Dihydroxynorephedrine; Levonordefrin; *l*-Nordefrin; Корбадрин.

(-)-2-Amino-1-(3,4-dihydroxyphenyl)propan-1-ol.

$C_9H_{13}NO_3$=183.2

CAS — 829-74-3 (corbadrine); 6539-57-7 (nordefrin); 61-96-1 (nordefrin hydrochloride).

UNII — V008L6478D.

Pharmacopoeias. In *US*.

USP 36: (Levonordefrin). A white to buff-coloured, odourless, crystalline solid. Practically insoluble in water; slightly soluble in alcohol, in acetone, in chloroform, and in ether; freely soluble in aqueous solutions of mineral acids.

Profile

Corbadrine is a sympathomimetic (p. 1507.3) that has been added to local anaesthetic preparations in dentistry to diminish absorption and to localise the effect; a concentration of 1 in 20 000 has been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations.

Used as an adjunct in:. *Canad.*: Isocaine; Polocaine; Scandonest; *S.Afr.*: Carbocaine; *USA*: Carbocaine with Neo-Cobefrin; Isocaine; Polocaine; Scandonest.

Pharmacopoeial Preparations

USP 36: Mepivacaine Hydrochloride and Levonordefrin Injection; Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection; Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection.

Coriander

Chinese Parsley; Coentro; Coriand.; Coriander Fruit; Coriander Seed; Coriandre; Coriandri Fructus; Coriandro; Fruto del cilantro; Kalendrų valsiai; Koriander; Koriandertermés; Koriandrový plod; Koriantari; Owoc kolendry; Perejil chino; Кориандр.

ATC Herb — HA03AW5019 (Coriandrum sativum: *fruit*).

UNII — 1OV56052IK.

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

Ph. Eur. 8: (Coriander). The dried cremocarp of *Coriandrum sativum*, containing not less than 0.3% v/w of essential oil,

calculated with reference to the dried substance. Protect from light.

The BP 2014 directs that when Powdered Coriander is prescribed or demanded material containing not less than 0.2% v/w of essential oil shall be dispensed or supplied.

Profile

Coriander is the source of coriander oil (below). It is a carminative and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Salutaris.

Multi-ingredient Preparations. *Arg.*: Wunderbalsam; *Austria*: Brady's-Magentropfen; Mariazeller; Planta Lax; *Belg.*: Eau Des Carmes; *Braz.*: Fitolax†; Florlax; Fontolax; Laxtam; Naturetti; Tamaril; Tamarine; Tamarine; *Canad.*: Digestol; Floradix Kindervital†; Formula T4†; *Fr.*: Azema†; Calmiflorine†; Mediflor Digestive No 3; Tisane Provencale no 5†; *Ger.*: Floradix Multipretten N; *Gr.*: Tamarine; *Hung.*: Babynos; Menofit; Salus Multipretten; Tamarinlax; *India*: Alka; Britesite; Gasex; Livomyn; Livomyn; *Ital.*: Cadifen; Cadimint; Dicalmir; Tamarine; *Mex.*: MD Lax; Naturetti; *Pol.*: Cholesol; Diges-Tonic; *Rus.*: Babynos (Бебинос); Cedoflor (Седофлор); Evalar (Эвалар); Kliophyt (Клиофит); Phytohepatol No 2 (Фитогепатол 2); Proctophytol (Проктофитол); Sodecor (Содекор); *S.Afr.*: Melissengeist†; Spiritus Contra Tussim Drops†; *Spain*: Agua del Carmen; Jarabe Manceau; Pruina; *Swed.*: Multipretten; *Switz.*: Pernisan; *UK*: Melissa Comp.; *Ukr.*: Bon-Apetit (Бон-Аппетит); Carminativum Babynos (Карминативум Бебинос); Intellan (Интеллан).

Homoeopathic Preparations. *Fr.*: Poconeol no 27; *UK*: Cough Drops.

Coriander Oil

Cilantro, aceite esencial de; Coriandre, huile essentielle de; Coriandri Aetheroleum; Coriandri Etheroleum; Kalendru eterinis aliejus; Korianderöl; Korianderolja; Koriandrová silice; Korianteriöljy; Ol. Coriand; Oleum Coriandri; Кориандровое Масло.

ATC Herb — HA03AW5018 (Coriandrum sativum: *essential oil*).
UNII — 7626GC95E5.

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

Ph. Eur. 8: (Coriander Oil). An essential oil obtained by steam distillation from the fruits of *Coriandrum sativum*. A clear colourless or pale yellow liquid, with the characteristic spicy odour. It contains not less than 65% and not more than 78% of linalol. Relative density 0.860 to 0.880. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Coriander Oil). The volatile oil obtained by steam distillation from coriander. Specific gravity 0.863 to 0.875. Soluble 1 in 3 of alcohol (70%). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Coriander oil is aromatic and carminative and is used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Floradix Multipretten N; Gastrysat†; *Hung.*: Salus Multipretten; *India*: Niltan; *Ital.*: Valda Propoli†; *Pol.*: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; *Rus.*: Espol (Эспол); *Swed.*: Multipretten.

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit; Compound Rhubarb Tincture;
USNF 31: Compound Orange Spirit.

Corn Silk

Barbas de Elote; Maiz, barba del; Stigma Maydis; Zea; Кукурузные Столбики С Рыльцами.

ATC Herb — HG04BW5043 (Zea mays: *style*).
UNII — 7D3VB244UX.

Pharmacopoeias. In *Fr.*

Profile

Corn silk, the stigma and style of maize (*Zea mays*) (Gramineae), has diuretic properties and is used for urinary-tract disorders including renal calculi.

Maize is widely used as a food and has also been used in herbal medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Insadol†; *Rus.*: Insadol (Инсадол); *Switz.*: Insadol†; *UK*: Protat.

Multi-ingredient Preparations. *Austral.*: Althaea Complex†; *Canad.*: Saw Palmetto Formula†; *Fr.*: Alpha Renol; Urotisan†; *Hung.*: Zeatax; *Pol.*: Neopoldanen†; *Spain*: Diurinat; *UK*: Elixir Damiana and Saw Palmetto; *Ukr.*: Urochol (Урохол)†; Urocran (Урокран).

Couch-grass

Agropyron; Chiendent; Chiendent, rhizome de; Dogs Grass; Grama; Grama del norte; Graminis rhizoma; Juolavehnänjuurakko; Kłącze perzu; Kvickrot; Pýrový oddenek; Quackgrass; Tarackbúza-gyökértörzs; Triticum; Twitch; Varpučių šakniastiebiai; Пырей Ползучий.

ATC Herb — HG04BW5010 (Elymus repens: *rhizome*); *HR05WA5007* (Elymus repens: *rhizome*).
UNII — 8K1MK5E1FY.

NOTE. Distinguish from Wheat, *Triticum aestivum* (see p. 2647.1).

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

Ph. Eur. 8: (Couch Grass Rhizome). The whole or cut, washed and dried rhizome of *Agropyron repens* (*Elymus repens*); the adventitious roots are removed. Protect from light.

Profile

Couch-grass is a mild diuretic that has been used in herbal medicine in the treatment of urinary-tract disorders. It contains glucose, mannitol, inositol, and triticin (a carbohydrate resembling inulin). The Latin binomials *Elytrigia repens* and *Triticum repens* have also been applied to couch-grass.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Urophyton; *Indon.*: Renalof.

Multi-ingredient Preparations. *Belg.*: Herbesan; *Canad.*: Bio Renal†; Floradix Tab†; *Fr.*: Alpha Renol; Drainuryl; Fibromyalgine; Herbesan; Hydrastart; Mediflor Diuretique No 4†; Obeflorine†; Tisane D'Ars†; Tisane de Sante†; Tisane Hepatique de Hoerdt†; Urotisan†; *Ger.*: Hevert-Blasen-Nieren-Tee N†; Renob Blasen- und Nierentee†; *Hung.*: Menofit; *Ital.*: Cistefi; Emmenotasi; Litostop; Tisana Kelemata; *Neth.*: Herbesan†; *Pol.*: Dentosept; Diabetofort; Diabetosol; Laxantol†; NeoFitolizyna†; *Spain*: Diurinat; *UK*: Antitis; Kas-Bah.

Homoeopathic Preparations. *Fr.*: Poconeol no 57; Poconeol no 79; *Ger.*: Urofossat.

Coumarin

1,2-Benzopyrone; 5,6-Benzo-α-pyrone; Cumarin; Cumarina; Kumaryna; Tonka Bean Camphor; Кумарин.

2*H*-1-Benzopyran-2-one.
$C_9H_6O_2$=146.1
CAS — 91-64-5.
UNII — A4VZ22K1WT.

Pharmacopoeias. In *Ger.*

Profile

Coumarin is the odorous principle of Tonka seed (Tonka or Tonquin bean); it may be prepared synthetically. Coumarin has been given to reduce excess tissue protein and associated fluid in the treatment of lymphoedema (see below). It has also been used as a fixative in perfumery and as a flavour. It is reported to be an immunostimulant and has been tried in the treatment of malignant neoplasms.

Coumarin derivatives are used as anticoagulants; coumarin itself is not an active anticoagulant.

Effects on the liver. Coumarin has been classified as hepatotoxic based on studies in *animals* and effects ranging from elevated liver enzymes to serious organ damage has been reported in humans. Seventeen of 2173 patients enrolled in a study of coumarin developed elevated liver enzyme values;[1] the majority of patients were given 100 mg coumarin daily for 1 month followed by 50 mg daily for 2 years. However, none of the patients developed permanent liver damage and liver enzyme values returned to normal in 5 patients who continued taking coumarin. Results from 5 studies supported by the Lymphoedema Association of Australia, in which patients received 400 mg daily for a mean duration of 14.6 months, showed 2 cases of hepatotoxicity among 1106 patients.[2] In the period of 14 months up to May 1995, the Australian Drug Evaluation Committee received 10 reports of suspected adverse reactions to coumarin,[3] including 6 cases of jaundice in women who had taken 400 mg daily for 1 to 4 months. Periportal and lobular necrosis were found on biopsy in 1 case and another had a fatal outcome due to massive hepatic necrosis.

Reports of hepatotoxicity have led to the withdrawal of coumarin in several countries.

1. Cox D, *et al.* The rarity of liver toxicity in patients treated with coumarin (1,2-benzopyrone). *Hum Toxicol* 1989; 8: 501–6.
2. Casley-Smith JR, Casley-Smith JR. Frequency of coumarin hepatotoxicity. *Med J Aust* 1995; 162: 391.
3. Anonymous. Lodema and the liver. *Aust Adverse Drug React Bull* 1995; 14: 11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/07/08)

Lymphoedema. Benzopyrones such as coumarin are reported to reduce excess protein in tissues with high-protein oedema, hence the use of coumarin in lymphoedema of various causes, including postmastectomy, and filarial lymphoedema and elephantiasis.[1-5] Evidence for its efficacy is, however, conflicting;[4,6] at best the action is slow and treatment may need to be given for 6 months to 2 years before any benefit is seen.

1. Jamal S, *et al.* The effects of 5,6 benzo-[a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India: preliminary results. *Ann Trop Med Parasitol* 1989; 83: 287–90.
2. Turner CS. Congenital lymphedema. *JAMA* 1990; 264: 518.
3. Casley-Smith JR, *et al.* Treatment of lymphedema of the arms and legs with 5,6-benzo-[α]-pyrone. *N Engl J Med* 1993; 329: 1158–63.
4. Casley-Smith JR, *et al.* Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-α-pyrone (coumarin). *BMJ* 1993; 307: 1037–41.
5. Casley-Smith JR. Benzo-pyrones in the treatment of lymphoedema. *Int Angiol* 1999; 18: 31–41.
6. Loprinzi CL, *et al.* Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 1999; 340: 346–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Esberiven; *Ital.*: Linfovenodren†.

Multi-ingredient Preparations. *Arg.*: Esberiven; Microsuy; *Braz.*: Angiolot; Varicoss; Venalot H; Venalot; *Ger.*: Venalot†; *Ital.*: Flebolider; *Mex.*: Venalot.

Homoeopathic Preparations. *Switz.*: Regenaplex Nr. 24b.

Coutarea Latiflora

Gopalchi.

ATC Herb — HG04BW5014 (Hintonia latiflora: *bark*); *HA09WA5014* (Hintonia latiflora: *bark*); *HA10BX5003* (Hintonia latiflora: *bark*); *HN02BG5006* (Hintonia latiflora: *bark*).

NOTE. The name copalchi has also been applied to *Croton niveus* (Euphorbiaceae).

Uses and Administration

Coutarea latiflora (*Hintonia latiflora*) is an ingredient of herbal remedies used in the management of diabetes mellitus.

Adverse Effects

For a report of hepatotoxicity associated with a preparation containing *Coutarea latiflora* see Centaury, p. 2473.2.

Rhabdomyolysis. Rhabdomyolysis and haemolysis occurred in a 58-year-old man 2 days after starting treatment with *Coutarea latiflora*.[1] The patient had a similar reaction 4 years earlier after taking the same product.

1. Roca B. Rhabdomyolysis and hemolysis after use of Coutarea latiflora. *Am J Med* 2003; 115: 677.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Sucontral†.

Cowberry

Alpine Cranberry; Arándano rojo; Lišć brusnicy (leaf); Mirtilo rojo; Red Whortleberry; Vitis Idaeae Folium (leaf); Брусника.

Pharmacopoeias. In *Pol.*

Profile

The leaves of the cowberry, *Vaccinium vitis-idaea* (Ericaceae), have astringent properties and have been used as a domestic remedy for diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Pol.*: Diuronis; Urosan†; *USA*: Prenate AM with Quatrefolic.

CR Gas

EA-3547; Gas CR.
Dibenz[b,f][1,4]oxazepine.
$C_{13}H_9NO = 195.2$
CAS — 257-07-8.

Profile

A riot-control gas with irritant and lachrymatory properties similar to those of CS gas (p. 2489.1); it is described as a tear gas. CR gas is reported not to be hydrolysed by water and therefore to be suitable for use in water cannons.

References.

1. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz(b,f)-1,4-oxazepine. *Toxicol Rev* 2003; 22: 103–10.
2. Carron PN, Yersin B. Management of the effects of exposure to tear gas. *BMJ* 2009; 338: 1554–8.

Cranberry

Arándano; Клюква.
UNII — 0MVO31Q3QS.

Pharmacopoeias. *US* includes a liquid preparation.

USP 36: (Cranberry Liquid Preparation). The bright red juice derived from the fruits of *Vaccinium macrocarpon* or *V. oxycoccos* (Ericaceae). It contains no added substances and is for manufacturing purposes only. pH between 2.4 and 2.6. Store at 2 degrees to 8 degrees.

Uses and Administration

Cranberry consists of the fruit of *Vaccinium macrocarpon*, the American cranberry or *V. oxycoccus*, the European cranberry. Cranberry juice has been reported to reduce the incidence of urinary-tract infections.

Urinary-tract infections. Cranberries and cranberry juice have been used widely for many years for both the prevention and treatment of urinary-tract infections. A systematic review[1] of available data concluded that there was some evidence that cranberry juice for prevention may decrease the number of symptomatic urinary-tract infections in women over a 12 month period, particularly those with recurrent infections. However, evidence for efficacy in the elderly is inconclusive, and currently lacking in patients with neurogenic bladder. The authors recommended further controlled studies in all susceptible patient groups, and also into more acceptable dosage formulations. However, another such review[2] assessing the efficacy of cranberry for treatment concluded that there was no good quality evidence to suggest that it is effective.

The mechanism of action of cranberry in preventing urinary-tract infections appears to be through inhibition of adhesion of uropathogens such as *Escherichia coli* to urinary-tract mucosa, thus reducing bacterial colonisation. There is reasonable evidence that this is due to its content of anthocyanidins and proanthocyanidins.[3]

1. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 02/12/09).
2. Jepson RG, *et al.* Cranberries for treating urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998 (accessed 02/12/09).
3. Guay DRP. Cranberry and urinary tract infections. *Drugs* 2009; 69: 775–807.

Interactions

For reports of interactions between cranberry juice and *warfarin*, see p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Urosedac; ***Chile***: Gelcive; ***Fr.***: Cys Control; GynDelta; Uriform; ***India***: Cranbe; ***Ital.***: Cistiflux; Ivumir; ***Singapore***: Seven Seas Cranberry Forte.

Multi-ingredient Preparations. ***Arg.***: Aulis; Uridon; Urosedac Probiotic; ***Austral.***: Advanced Urinary Tract Care; Cranberry 10,000; Cranberry Complex†; Cranberry Complex; Cranbiotic Super†; Extralife Uri-Care†; Flavonoid Complex; ***Canad.***: Prostease; ***Fr.***: Acyprost; Duab; Feminabiane Confort Urinaire; Gyn-Delta PRIM; Gynelys; Prostaform; ***Hong Kong***: Prostease; ***Ital.***: Cistefi; Litostop; Rubis; ***Pol.***: Diabetosol; Urosept; ***Rus.***: Evalar (Эвалар); Urokam (Урокам); ***Ukr.***: Ektis (Эктис); Lekran (Лекран); Nephrocare (Нефрокеа); Uro-Control (Уро-Контрол); Urocran (Урокран); ***Venez.***: Diamel; Optibiol.

Crataegus

Aubépine; Aubépine, baie d' (hawthorn berries); Aubépine, feuille et fleur d' (hawthorn leaf and flowers); Biancospino; Calabrice; Crataegi folium cum flore (hawthorn leaf and flowers); Crataegi fructus (hawthorn berries); Crataegi Inflorescentia (hawthorn leaf and flowers); English Hawthorn; Espinalbo; Espino albar; Espino blanco; Galagonyatermés (hawthorn berries); Gudobelių vaisiai (hawthorn berries); Hagtornsbär (hawthorn berries); Haw; Hlohový plod (hawthorn berries); Kwiatostan głogu (hawthorn leaf and flowers); May; Mehlbeerbaum; Orapihlajanmarja (hawthorn berries); Owoc głogu (hawthorn berries); Pilriteiro; Weissdorn; Whitethorn; Боярышник.
ATC — C01EB04.
ATC Vet — QC01EB04.
ATC Herb — HC01EB5008 (Crataegus monogyna; flower); HC01EB5004 (Crataegus laevigata; leaf); HC01EB5003 (Crataegus laevigata; fruit); HC01EB5002 (Crataegus laevigata; flower); HC01EB5012 (Crataegus monogyna; leaf with flower with fruit); HC01EB5010 (Crataegus monogyna; leaf); HC01EB5013 (Crataegus monogyna; leaf with fruit); HC01EB5009 (Crataegus monogyna; fruit); HC01EB5011 (Crataegus monogyna; leaf with flower); HC01EB5007 (Crataegus laevigata; leaf with fruit); HC01EB5006 (Crataegus laevigata; leaf with flower with fruit); HC01EB5005 (Crataegus laevigata; leaf with flower).
UNII — 6OM09RPY36 (hawthorn leaf with flower); Q21UUL2105 (crataegus fruit).

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

Ph. Eur. 8: (Hawthorn Berries; Crataegi Fructus). The dried false fruits of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or a mixture of these false fruits. They contain not less than 0.06% of procyanidins, calculated as cyanidin chloride ($C_{15}H_{11}ClO_6 = 322.7$) with reference to the dried drug.

Ph. Eur. 8: (Hawthorn Leaf and Flower; Crataegi Folium cum Flore). The whole or cut, dried flower bearing branches of *Crataegus oxyacantha* (*C. laevigata*), or *C. monogyna*, or their hybrids or, more rarely, other European *Crataegus* species including *C. pentagyna*, *C. nigra*, and *C. azarolus*. It contains not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12} = 464.4$) calculated with reference to the dried drug.

USP 36: (Hawthorn Leaf with Flower). The dried tips of the flower-bearing branches up to 7 cm in length of *Crataegus monogyna* or *C. laevigata*, also known as *C. oxyacantha* (Rosaceae). It contains not less than 0.6% of *C*-glycosylated flavones, expressed as vitexin ($C_{21}H_{20}O_{10} = 432.4$), and not less than 0.45% of *C*-glycosylated flavones, expressed as hyperoside, calculated with reference to the dried drug. Protect from light.

Profile

Crataegus contains flavonoid glycosides with cardiotonic properties similar to those of digoxin (p. 1353.3). Crataegus is used in herbal medicine.

Homoeopathy

Crataegus has been used in homoeopathic medicines under the following names: Crataegus oxyacantha; Crat. oxy.

Crataegus is used in herbal medicine for cardiovascular disorders.[1-4] A systematic review[5] of controlled studies concluded that it shows significant benefit compared with placebo as an adjunctive treatment for chronic heart failure. However, results from a large randomised, double-blind, placebo-controlled, multicentre study (the SPICE trial) involving 2681 patients showed that a crataegus extract used as adjunctive treatment for heart failure had no significant effect on measures of primary outcome defined as a composite of cardiac death, non-fatal myocardial infarction, and hospitalisation due to progressive heart failure, although it might reduce sudden cardiac death in patients with left ventricular ejection fraction between 25 and 35%.[6] Crataegus is rarely associated with serious adverse affects, although the authors of another systematic review[4] noted that problems may occur with its unsupervised use, especially if given with other drugs.

1. Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. *Am J Health-Syst Pharm* 2002; 59: 417–22.
2. Chang Q, *et al.* Hawthorn. *J Clin Pharmacol* 2002; 42: 605–12.
3. WHO. Folium cum Flore Crataegi. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/9.html (accessed 04/02/10)
4. Daniele C, *et al.* Adverse-event profile of Crataegus spp.: a systematic review. *Drug Safety* 2006; 29: 523–35.
5. Guo R, *et al.* Hawthorn extract for treating chronic heart failure. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/04/08).
6. Holubarsch CJF, *et al.* The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: the SPICE trial. *Eur J Heart Fail* 2008; 10: 1255–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Bericard; Crataefortan; Crataegan; Crataegutt; ***Belg.***: Aubeline; ***Braz.***: Dekatin; ***Chile***: Cratenox; ***Cz.***: Caj z Hlohu; Hloh†; ***Fr.***: Aubeline†; Cardiocalm; ***Ger.***: Ardeycordal mono; Born†; Chronocard N; Cordapur Novo†; Craegium†; Cratae-Loges; Crataegutt; Dr Niedermaier Herztonikum†; Esbericard novo; Faros; Koro-Nyhadin; Natucor; Orthangin novo†; Oxacant-mono; Protecor Herz-Schutz†; Protecor novo†; Regulacor-POS†; Septacord mono†; Stenocrat mono; ***Pol.***: Cardiplant; Chronocard; Cratonic; ***Rus.***: Doppelherz Cardiovital (Доппельгерц Кардиовитал); Novo-Passit (Ново-Пассит); Phytorelax (Фиторелакс); ***Singapore***: Crataegutt†; ***Switz.***: Cardiodyn; Cardiplant; Crataegisan; Crataegitan; Faros; Kardionin; Vitacor; ***Ukr.***: Cardiplant (Кардиплант)†.

Multi-ingredient Preparations. ***Arg.***: Barium Jodatum Oligoplex; Hepatodirectol; Passacanthine; Sequals G; ***Austral.***: Asa Tones†; Bioage Peripheral†; ChelaCo; Coleus Complex†; Dan Shen Compound; For Peripheral Circulation Herbal Plus Formula 5†; ***Austria***: Korodin; Rutiviscal; Wechseltee St Severin; ***Belg.***: Natudor; Sedinal; Seneuval; ***Braz.***: Calman; Calmiplan; Floriny; Pasalix; Pasic; Passiflorine; Serenus; Sominex; ***Canad.***: Calmane; Floradix Tab†; Salusan†; ***Chile***: Armonyl; ***Cz.***: Alvisan Neo; Doppelherz Energie-Tonikum†; Fytokliman Planta; Hypotonicka†; Novo-Passit; Valofyt Neo†; ***Fr.***: Biocarde; Calmiflorine†; Euphytose; Lenicalm†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Natudor; Neuroflorine†; Neuropax†; Nicoprive; Nocvalene†; Okimus; Omezelis; Passiflorine; Passinevryl†; Provencale No 4†; Santane N_9; Sedalozia†; Sedatif Tiber†; Sedopal; Spasmine; Sympathyl; Sympavagol†; Tisane Provencale no 4†; Tranquital; Vagostabyl; ***Ger.***: Antihypertonicum S; Bomacorin; Cardio-Kreislauf-Longoral; Ilja Rogoff; Korodin; Oxacant-sedativ; Passin; Protecor; Saluscor Herz-Schutz†; Septacord; Tornix; ***Gr.***: Passiflorine; Passinevrol; ***Hung.***: Antipoll; Crategil; Doppelherz Energie Tonikum N; Kardalept; Mensesyl; Salus Herz-Schutz; Sam-Ginseng Royal; Sanhelios 333; Worishofener; ***India***: Nutiva-Lyco; ***Indon.***: Procardio†; ***Israel***: Nerven-Dragees; Passiflora; ***Ital.***: Anevrasi; Bioestril Ginseng; Controller; Lenicalm; Mirtiros; Noctis; Parvisedil; Passiflorine; Sedatol; Sedatol; Sedopuer F; Vagostabil; ***Jpn***: Keihito; ***Malaysia***: Circarol; ***Mex.***: Ifupasil; ***Philipp.***: Circulan; ***Pol.***: Alliorut†; Biovital N†; Cardiactiv; Cardiobonisol; Cardiol C; Cardiotonic; Cravisol; Doppelherz Energovital Tonik K; Doppelherz Energovital Tonik†; Fitoven; Gerovital Zdrovit; Ginkgocard†; Herbaton†; Kelicardina; Melis-Tonic; Melisal; Melissed; Neocardina; Neospasmina; Neospasmol†; Nerwobonisol; Nerwonal; Passibil; Passispasmin; Passispasmol†; Perfocrat†; Sedomix; Tabletki Tonizujace; Venoforton; ***Rus.***: Biovital (Биовитал); Bromenval (Броменвал); Cardiovalen (Кардиовален); Cedoflor (Седофлор); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Evalar (Эвалар); Herbion Drops for the Heart (Гербион Сердечные Капли)†; Kliophyt (Клиофит); Passifit (Пассифит); Phyto Novo-Sed (Фито Ново-Сед); Sympathyl (Симпатил); Valemidin (Валемидин); ***Singapore***: Cardio-Essentials; ***Spain***: Passiflorine; Sedonat; Valeriana Leo; ***Switz.***: Arterosan Plus†; Cardiaforce; Cardiophyt A; Circulan†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Gouttes pour le coeur et les nerfs; Ipasin; Passiflor; Tai Ginseng†; Tisane pour le coeur et la circulation; Valverde Coeur; ***Ukr.***: Central-B (Централ-В); Cratal (Кратал); Gerovital Dr. Theiss (Геровитал Др. Тайсс); Herbion Drops for Heart (Гербион Сердечные Капли)†; Neokardil (Неокардил); Normoton (Нормотон); Novo-Passit (Ново-Пассит); Persen Cardio (Персен Кардио); Sedafiton (Седафитон); Sedavit (Седавит); Vitokan (Витокан); ***USA***: Bioflex; Cardio Tone; Cardiopress; Flexgen; ***Venez.***: Equaliv; Ervostal; Pasidor; Pasifluidina; Passiflorum.

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; ***Austria***: Arnica Med Complex; Aurumheel; Cactus compositum; Cefavora; Cora; Corasan; Cralonin; Homviocorin; Homviotensin; Pumpan; Rytmopasc; Selenium Med Complex; Valerianaheel; ***Canad.***: Aurumheel†; Tyglan†; ***Chile***: Melinerv; ***Fr.***: Adenocynesine†; Boripharm No 41; Calmodren; Crataegus Complexe No 15; Homeogene 14†; Hydrastis Compose; Kalium Iodatum Complexe No 84†; Santaherba; Sclerocalcine; Soludor; Strophantus Compose; ***Ger.***: Aktivon; Angioton H; Angioton S†; Antihypertonicum-Tropfen N†; Aurum-Gastreu S R2; Cardioject; Cardioselect N; Cefangipect H†; Cefangipect†; Cefavora Cor; Cefavora†; Confludin N; Conva-cyl Ho-Len-Complex; Convallocor; Convallysan M; Convastabil; Cor-loges; Cororell; Corselect N; Corvipas SL; Cralonin; Crataegus comp; Crataegus comp; Crataegus Herzcomplex; Diacard; Emocrat N†; Goldtropfen S; Habstal-Cor N; HanoCor N; Hevert-Activon Kreislauftropfen†; Homviocorin spezial; Homviotensin; Hypotonie-Gastreu R44; Infi-Camphora; Kattwicor; Korolinda; Lowe-Komplex Nr 10; Lowe-Komplex Nr 3; Naranocor HM; Oto-cyl Ho-Len-Complex; Pectapas CPL; Pectapas SL; Pectapas; Phonix Silybum spag; Plantacard N; Procordal; RauwolfiaViscomp; Roth's Rotacard; Rytmopasc; Santa Flora S; Schworocard; Steicardin N†; Strophanthus comp; Uwobletten Arteriosklerose-Complex†; ***Hung.***: Aurumheel; ***Neth.***: Cralonin H; Cralonin; Nervofleur; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); Pumpan (Пумпан); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Cralonin; Gouttes d'Or; ***Ukr.***: Aurocard (Аурокард); Cefavora (Цефавора); Homviocorin-N (Хомвиокорин-N); Homviotensin (Хомвиотензин); Pumpan (Пумпан).

Pharmacopoeial Preparations
Ph. Eur.: Hawthorn Leaf and Flower Dry Extract.

Creatine

Креатин.
N-(Aminoiminomethyl)-*N*-methylglycine.
$C_4H_9N_3O_2 = 131.1$

CAS — 57-00-1 (creatine); 6020-87-7 (creatine monohydrate).
UNII — MU72812GK0 (creatine); 9603LN7R2O (creatine monohydrate).

Creatine Phosphate

Creatina, fosfato de; Creatine Phosphoric Acid; Fosfocreatine; Phosphocreatine; Креатинфосфат.
N-[Imino(phosphonoamino)-methyl]-*N*-methylglycine.
$C_4H_{10}N_3O_5P$=211.1
CAS — 67-07-2 (creatine phosphate); 922-32-7 (creatine phosphate disodium).
ATC — C01EB06.
ATC Vet — QC01EB06.
UNII — 020IUV4N33.

Profile

Creatine is an endogenous substance found mainly in skeletal muscle of vertebrates. Creatine phosphate and its disodium salt have been tried in the treatment of cardiac disorders. Creatine phosphate has also been added to cardioplegic solutions. Creatine monohydrate has been tried in metabolic disorders and used as a dietary supplement. It is also under investigation for the treatment of Parkinson's disease, motor neurone disease (p. 2605.2), Duchenne muscular dystrophy, and Huntington disease.

References.
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2. Ferraro S, *et al.* Acute and short-term efficacy of high doses of creatine phosphate in the treatment of cardiac failure. *Curr Ther Res* 1990; 47: 917–23.
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8. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol Rev* 2001; 53: 161–76.
9. Mazzini L, *et al.* Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. *J Neurol Sci* 2001; 191: 139–44.
10. Groeneveld JG, *et al.* A randomized sequential trial of creatine in amyotrophic lateral sclerosis. *Ann Neurol* 2003; 53: 437–45.
11. Persky AM, *et al.* Pharmacokinetics of the dietary supplement creatine. *Clin Pharmacokinet* 2003; 42: 557–74.
12. Shefner JM, *et al.* A clinical trial of creatine in ALS. *Neurology* 2004; 63: 1656–61.
13. Ellis AC, Rosenfeld Jo. The role of creatine in the management of amyotrophic lateral sclerosis and other neurodegenerative disorders. *CNS Drugs* 2004; 18: 967–80.
14. Tarnopolsky MA, *et al.* Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. *Neurology* 2004; 62: 1771–7.
15. Pline KA, Smith CL. The effect of creatine intake on renal function. *Ann Pharmacother* 2005; 39: 1093–6.
16. Hersch SM, *et al.* Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. *Neurology* 2006; 66: 250–2.
17. Bender A, *et al.* Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. *Neurology* 2006; 67: 1262–4.
18. Kley RA, *et al.* Creatine for treating muscle disorders. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2007 (accessed 18/04/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Neoton (里尔统); *Cz.*: Neoton; *Ital.*: Creatile; *Pol.*: Neoton; *Rus.*: Neoton (Неотон).

Multi-ingredient Preparations. *Arg.*: Gel Fitotonico; *Indon.*: Hemaviton Action; *Ital.*: Anasten Plus; Creavit; Enercomplex; Fortium; NeoBros C; Neovis; Vitalmix Fast; *Switz.*: Carnidyn.

Crotalaria

Кроталярия.

Profile

Crotalaria spp. have been used in herbal teas but liver damage has been reported after their ingestion, possibly due to their content of pyrrolizidine alkaloids.

CS Gas

CS Gazi; CS Spray; Gas CS.
$C_{10}H_5ClN_2$=188.6
CAS — 2698-41-1.

Profile

CS gas (more properly CS spray) is the name commonly given to a particulate dispersion of α-(*o*-chlorobenzylidene) malonitrile, used as a riot-control agent or 'tear gas'. Its toxic effects include irritation of the eyes and nose, with copious lachrymation and rhinorrhoea; blepharospasm; a burning sensation of the mouth and throat; tightness in the chest, with difficulty in breathing; coughing; an increase in salivation; and retching and vomiting. These effects usually disappear within 15 minutes after exposure ends. The effects of pre-existing disease of the respiratory tract may be exacerbated. Erythema and blistering of the skin may occur.

If symptoms persist, the patient should be removed to a well ventilated area. Treatment is symptomatic. Contaminated skin may be washed with soap and water, but only if symptoms persist since exposure to water may initially exacerbate symptoms. If contamination of the eyes has been severe they should be irrigated with physiological saline or water.

References.
1. Hu H, *et al.* Tear gas—harassing agent or toxic chemical weapon? *JAMA* 1989; 262: 660–3.
2. Yih J-P. CS gas injury to the eye. *BMJ* 1995; 311: 276.
3. Gray PJ. Treating CS gas injuries to the eye: exposure at close range is particularly dangerous. *BMJ* 1995; 311: 871.
4. Jones GRN. CS sprays: antidote and decontaminant. *Lancet* 1996; 347: 968–9.
5. Anderson PJ, *et al.* Acute effects of the potent lacrimator o-chlorobenzylidene malononitrile (CS) tear gas. *Hum Exp Toxicol* 1996; 15: 461–5.
6. Anonymous. "Safety" of chemical batons. *Lancet* 1998; 352: 159.
7. Varma S, Holt PJ. Severe cutaneous reaction to CS gas. *Clin Exp Dermatol* 2001; 26: 248–50.
8. Nathan R, *et al.* Long-term psychiatric morbidity in the aftermath of CS spray trauma. *Med Sci Law* 2003; 43: 98–104.
9. Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev* 2003; 22: 103–10.
10. Carron PN, Yersin B. Management of the effects of exposure to tear gas. *BMJ* 2009; 338: 1554–8.

Cubeb

Cubeb Berries; Cubeb Fruit; Cubeba; Java Pepper; Tailed Pepper; Кубеба.
UNII — Z99L7429MA.

Profile

The unripe seeds of cubeb, *Piper cubeba* (Piperaceae), are the source of cubeb oil, which is used in perfumery and aromatherapy. Cubeb is an ingredient of various herbal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Pervivo; *Hung.*: Bittner; *Pol.*: Pervivo; *Rus.*: Doktor Mom (Доктор Мом); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *Ukr.*: Doktor Mom (Доктор Мом сироп).

Homoeopathic Preparations. *Switz.*: Regenaplex Nr. 49a.

Cucurbita

Abóbora; Calabacera; Calabaza, semillas de; Kürbissamen; Melon Pumpkin Seeds; Pepo; Pipas de la calabaza; Semence de Courge; Семена Тыквы.
*ATC Herb. — HP02DW5001 (*Cucurbita pepo*: seed); HG04CW5001 (*Cucurbita pepo*: seed).*

Pharmacopoeias. In *Ger.*

Profile

Cucurbita consists of the seeds of *Cucurbita pepo* (Cucurbitaceae) or related species. It was formerly used for the expulsion of tapeworms (*Taenia*).

It is an ingredient of several herbal preparations used in urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Lefkur; *Fr.*: VITIX; *Ger.*: Cysto-Urgenin†; Granu Fink Kurbiskern†; Granu Fink Prosta forte; Nomon mono; Prosta Fink forte†; Urgenin Cucurbitae oleum; Uvirgan mono†; Vesiherb; *Hung.*: Peponen; *Indon.*: Inkurin; *Pol.*: Peponen; Peposterol; *Rus.*: Peponen (Пепонен); Tycveolum (Тыквеол); Vitanorm (Витанорм); *Switz.*: Kurbin†; *Ukr.*: Peponen (Пепонен).

Multi-ingredient Preparations. *Arg.*: Cellskinlab Phyto Spot; Clean-AC; Cleanance; Cleanance; Cleanance; Prostafit; *Austral.*: In-Control; ProstaCo; *Canad.*: Optomega; Prosta Ease; Prostease; Saw Palmetto Formula†; *Chile*: Clean-AC; Cleanance; Cleanance; *Fr.*: Acyprost; Alpharegul Femme; Alpharegul Homme; Androlistica; Cleanance K; Cleanance; Prostabiol; ProstaSecurA; *Ger.*: Granu Fink Blase Kurbiskern†; Granu Fink Femina; Granu Fink Prosta; Prostamed; *Hong Kong*: Prostease; *Hung.*: Uroherb; *Indon.*: Soprost†; *Ital.*: Biomineral 5-Alfa; *Philipp.*: Castoria; *Port.*: Bioclin Sebo Care; *Rus.*: Bioprost (Биопрост); *Singapore*: Androlistica; *Switz.*: Granu Fink Prosta†; Herbaprosta-Caps N†; *UK*: Ymea; *Ukr.*: Prostamed (Простамед); *Venez.*: Argeal.

Homoeopathic Preparations. *Fr.*: Sels Calcaires Nutritifs; *Ger.*: Vomistop; *S.Afr.*: Aufbaukalk I†; *UK*: Apatite.

Curcuminoids

Куркуминоиды.

Pharmacopoeias. In *US*.

USP 36: (Curcuminoids). A partially purified natural complex of diaryl heptanoid derivatives isolated from turmeric (*Curcuma longa*). It contains not less than 95.0% of curcuminoids, calculated on the dried basis, as the sum of curcumin, desmethoxycurcumin, and bisdesmethoxycurcumin. It contains not less than 70.0% and not more than 80.0% of curcumin, not less than 15.0% and not more than 25.0% of desmethoxycurcumin, and not less than 2.5% and not more than 6.5% of bisdesmethoxycurcumin. Protect from light and moisture.

Profile

Curcuminoids are phenolic compounds found in turmeric (p. 2218.1). The principal ones are curcumin (p. 2180.1), desmethoxycurcumin, and bisdesmethoxycurcumin, all of which contribute to the yellow colour of turmeric. Curcuminoids are used as dietary supplements. There is considerable interest in potential medicinal uses, and curcuminoids have been reported to have anti-angiogenic, anti-cancer, anti-inflammatory, antimicrobial, antioxidant, anti-thrombotic, and immunomodulatory actions. Hydrogenation of curcuminoids produces tetrahydrocurcuminoids, which are colourless and therefore have potential uses in colourless food products and cosmetics.

References.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Longin.

Multi-ingredient Preparations. *India*: Melaglow; *Indon.*: Apecur; Bevita; Biofos†; Heparviton NF; Heparviton; Hepatin; Prokids; Proliver; Reliv†; Vitagrow; Ximun.

Pharmacopoeial Preparations
USP 36: Curcuminoids Capsules; Curcuminoids Tablets.

Cusparia

Angostura; Angostura Bark; Carony Bark; Cusparia Bark; Ангостура.
UNII — 104010O5VU.

NOTE. 'Angostura Bitters' (*Dr. J.G.B. Siegert*) contains gentian and various aromatic ingredients but no cusparia; it is named after the town in which it was first made.

Profile

Cusparia, the bark of *Galipea officinalis* (Rutaceae), has been used as a bitter.

Cyanoacrylate Adhesives

Cianoacrilato, adhesivos de; Цианакрилатные Клеи.

Bucrilate *(rINN)*

Bucrilato; Bucrilatum; Bucrylate (USAN); Bucrylate; IBC; IBCA; Isobutyl Cyanoacrylate; Букрилат.
Isobutyl 2-cyanoacrylate.
$C_8H_{11}NO_2$=153.2
CAS — 1069-55-2.
UNII — 2HJV1F859Z.

Enbucrilate *(BAN, rINN)*

n-Butyl Cyanoacrylate; Enbucrilato; Enbucrilatum; NBCA; Энбукрилат.
Butyl 2-cyanoacrylate.
$C_8H_{11}NO_2$=153.2
CAS — 6606-65-1.
UNII — F8CEP82QNP.

The symbol † denotes a preparation no longer actively marketed

Ethyl Cyanoacrylate

ECA; Этилцианакрилат.
Ethyl 2-cyanoacrylate.
$C_6H_7NO_2$=125.1
CAS — 7085-85-0.
UNII — 2G95FOH7SF.

Mecrilate *(rINN)*

Cyanoacrylate; MCA; Mécrilate; Mecrilato; Mecrilatum; Mecrylate (USAN); Mecrylate; Мекрилат.
Methyl 2-cyanoacrylate.
$C_5H_5NO_2$=111.1
CAS — 137-05-3.
UNII — WN7979561R.

Ocrilate *(rINN)*

Ocrilato; Ocrilatum; Ocrylate (USAN); Ocrylate; Окрилат.
Octyl 2-cyanoacrylate.
$C_{12}H_{19}NO_2$=209.3
CAS — 6701-17-3.
UNII — 6C655P1XVG.

Uses and Administration

Several cyanoacrylate compounds have been used as surgical tissue adhesives including bucrilate, enbucrilate, ethyl cyanoacrylate, mecrilate, and ocrilate.

Some cyanoacrylates are used for household purposes and as nail fixatives and others have been investigated as tubal occlusive agents for female sterilisation, for sclerotherapy in bleeding gastric varices (see under Monoethanolamine, p. 2563.1), and for embolisation of intracranial vascular lesions. Cyanoacrylate adhesives have also been used to plug corneal perforations until donor tissue is available.

References to the use of cyanoacrylate adhesives,[1-10] including bucrilate,[1,2] enbucrilate,[3,4] and ocrilate.[5-9]

1. Kind R, *et al.* Bucrylate treatment of bleeding gastric varices: 12 years' experience. *Endoscopy* 2000; 32: 512–9.
2. Shepler TR, Seiff SR. Use of isobutyl cyanoacrylate tissue adhesive to stabilize external eyelid weights in temporary treatment of facial palsies. *Ophthal Plast Reconstr Surg* 2001; 17: 169–73.
3. Schonauer F, *et al.* Use of Indermil tissue adhesive for closure of superficial skin lacerations in children. *Minerva Chir* 2001; 56: 427–9.
4. Sinha S, *et al.* A single blind, prospective, randomized trial comparing n-butyl 2-cyanoacrylate tissue adhesive (Indermil) and sutures for skin closure in hand surgery. *J Hand Surg (Br)* 2001; 26: 264–5.
5. Kutcher MJ, *et al.* Evaluation of a bioadhesive device for the management of aphthous ulcers. *J Am Dent Assoc* 2001; 132: 368–76.
6. Puri P. Tissue glue aided lid repositioning in temporary management of involutional entropion. *Eur J Ophthalmol* 2001; 11: 211–4.
7. Bernard L, *et al.* A prospective comparison of octyl cyanoacrylate tissue adhesive (dermabond) and suture for the closure of excisional wounds in children and adolescents. *Arch Dermatol* 2001; 137: 1177–80.
8. Mattick A, *et al.* A randomised, controlled trial comparing a tissue adhesive (2-octylcyanoacrylate) with adhesive strips (Steristrips) for paediatric laceration repair. *Emerg Med J* 2002; 19: 405–7.
9. Magee WP, *et al.* Use of octyl-2-cyanoacrylate in cleft lip repair. *Ann Plast Surg* 2003; 50: 1–5.
10. Singer AJ, *et al.* The cyanoacrylate topical skin adhesives. *Am J Emerg Med* 2008; 26: 490–6.

Adverse Effects and Treatment

Cyanoacrylate adhesives are considered to be non-toxic since they set within seconds of exposure to air. However, heat is evolved on solidification of cyanoacrylate and in rare cases may cause tissue burns. Mild irritation may occur particularly when bonded surfaces are separated mechanically, and contact dermatitis may occur after chronic exposure. Ocular contact with cyanoacrylate adhesives causes eyelids to seal rapidly and may also strip the skin; corneal abrasion, conjunctivitis, and loss of eyelashes may also occur.

In the event of accidental adhesion of the skin the bonded surfaces may be separated after application of acetone, prolonged soaking in warm (not hot) soapy water, and/or mixtures of alcohol and water. Application of liquid paraffin may help in removal from the skin. If necessary, the surfaces may be peeled or rolled apart with the aid of a spatula; attempts should not be made to pull the surfaces directly apart. Acetone and alcohol should not be used near or in the eyes. Solvents such as nitromethane, toluene, or xylene may be used to aid skin detachment from solid objects. Solvents should be used with care and should not be introduced into the oropharynx. Eyelids stuck together or bonded to the eyeball should be washed thoroughly with saline or water at room temperature for 15 minutes and a gauze patch applied; the eye will open without further action in 1 to 4 days. Manipulative attempts to open the eyes should not be made. Although cyanoacrylate introduced into the eyes may cause double vision and lachrymation there is usually no residual damage. If lips are accidentally stuck together plenty of warm water should be applied and maximum wetting from saliva inside the mouth encouraged. Lips should be peeled or rolled apart and not pulled. Adhesive introduced into the mouth solidifies and adheres, but saliva will lift the adhesive in ½ to 2 days. Care should be taken to avoid choking.

Reports of inadvertent application of cyanoacrylate adhesives to the eyes,[1,2] mouth,[3] and ears.[4,5] Pulmonary embolisation of ocrilate has been reported[6] when it was used to obliterate gastric varices in a patient.

1. Lyons C, *et al.* Superglue inadvertently used as eyedrops. *BMJ* 1990; 300: 328.
2. DeRespinis PA. Cyanoacrylate nail glue mistaken for eye drops. *JAMA* 1990; 263: 2301.
3. Cousin GCS. Accidental application of cyanoacrylate to the mouth. *Br Dent J* 1990; 169: 293–4.
4. O'Donnell JJ, *et al.* Cyanoacrylate adhesive mistaken for ear drops. *J Accid Emerg Med* 1997; 14: 199.
5. Perraud R. A novel approach to the removal of superglue from the ear. *J Laryngol Otol* 2001; 115: 901–2.
6. Rickman OB, *et al.* Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004; 79: 1455–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dermabond†; *Gr.*: Histoacryl; *India*: Cutseal; Gesika; *UK*: Dermabond; Histoacryl; Indermil; LiquiBand; SuperSkin.

Multi-ingredient Preparations. *Ger.*: Epiglu; *Irl.*: Epiglu†; *UK*: Epiglu.

Cyclamen

Cyclamen d'Europe.
UNII — G728143D8Q.

NOTE. The name Cyclamen Europaeum has been applied to several related species of *Cyclamen* but strictly applies to *C. purpurascens*. The name Sowbread is applied to several species of *Cyclamen* but usually applies to *C. hederifolium*.

Profile

The tuber of *Cyclamen purpurascens* (*C. europaeum*) (Primulaceae) has been used in herbal medicine for a range of indications; it is reported to be a drastic purgative. An extract of the tuber has been used for sinusitis.

The related species *C. hederifolium* has also been used.

Homoeopathy

Cyclamen has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Nasodren; *Rus.*: Sinuforte (Синуфорте).

Homoeopathic Preparations. *Austria*: Mastodynon; Migrenopas†; *Canad.*: Alfalfa Tonic; Formula DM 210†; Headache & Migraine L77; Headache & Migraine; Homeo-Form MI†; *Cz.*: Hormeel S; Mastodynon; *Fr.*: Phapax; *Ger.*: Antimast TN†; Antimigren; Biodolor; Cefanalgin†; Cephaloplant†; Dolfin; DolorA; Femin-Do; Mastodynon; Neuro-Do; Pflugerplex Gelsemium; *Hung.*: Hormeel S; *Neth.*: Homeocare Nervo; Hormeel H; Hypertilite; Mastodynon†; *Rus.*: Hormeel SN (Гормель СН); Mastodynon (Мастодинон); *Switz.*: Menstruasan; Multiplex 1; *Thai.*: Mastodynon†; *Ukr.*: Capadol (Кападол); Mastodynon (Мастодинон).

Cyclobutyrol Sodium *(rINNM)*

Ciclobutirol sódico; Cyclobutyrol Sodique; Natrii Cyclobutyrolum; Натрий Циклобутирол.
Sodium 2-(1-hydroxycyclohexyl)butyrate.
$C_{10}H_{17}NaO_3$=208.2
CAS — 512-16-3 (cyclobutyrol); 1130-23-0 (cyclobutyrol sodium).
ATC — A05AX03.
ATC Vet — QA05AX03.
UNII — 9EA1G6PR44.

Profile

Cyclobutyrol sodium is a choleretic that has been given orally. Cyclobutyrol betaine, cyclobutyrol calcium, and cyclobutyrol nicotinamide have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Sugarbil†.

Cyclovalone *(rINN)*

Ciclovalona; Cyclovalonum; Циклованон.
2,6-Divanillylidenecyclohexanone.
$C_{22}H_{22}O_5$=366.4
CAS — 579-23-7.
UNII — 6M4YJ3FA16.

Profile

Cyclovalone has been used as a choleretic and for dyspepsia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Vanilone.

Cymene

Cimeno; *p*-Cimeno; *p*-Cymene; *p*-Cymol; *p*-Cymen; Цимол; Цимен.
4-Isopropyl-1-methylbenzene; 4-Isopropyltoluene.
$C_{10}H_{14}$=134.2
CAS — 25155-15-1; 99-87-6 (p-cymene).
UNII — 1G1C8T1N7Q.

Profile

Cymene is used in perfumery. It has also been used as a topical local analgesic for the relief of pain in rheumatic conditions.

Cynara

Alcachofa; Alcachôfra; Alcacil; Artichaut; Artichaut, feuille d'; Artichoke Leaf; Artičokový list; Artischockenblätter; Cynarae folium; Liść karczocha; Лист Артишока.
ATC Herb — HG04BW5007 (Cynara cardunculus: *leaf*); *HA05AW5007* (Cynara cardunculus: *leaf*); *HC10AW5006* (Cynara cardunculus: *leaf*).
UNII — B71UA545DE.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract prepared from the leaves.

Ph. Eur. 8: (Artichoke Leaf). The whole or cut, dried leaf of *Cynara cardunculus* (*C. scolymus*). It contains a minimum 0.8% of chlorogenic acid ($C_{16}H_{18}O_9$=354.3), calculated with reference to the dried drug. Protect from light.

Profile

Cynara, the leaf of the globe artichoke, *Cynara scolymus* (Compositae), is reputed to have diuretic and choleretic properties. It may also have some hypolipidaemic activity. Cynara is the source of cynarine (p. 2491.1).

References.

1. Joy JP, Haber SL. Clinical uses of artichoke leaf extract. *Am J Health-Syst Pharm* 2007; 64: 1904–9.
2. Wider B, *et al.* Artichoke leaf extract for treating hypercholesterolaemia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 04/02/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Chofitol; Cynarex; Lorhepatic; *Austria*: Cynarix; Hepar-POS†; *Belg.*: Cholaplus; Cynarol; Hebucol; *Braz.*: Alcachofrax; Alcagest; Chophytol; *Fr.*: Chophytol; Hepanephrol; *Ger.*: aar gamma N; Ardeycholan; Aristochol Gallekapsein†; Cefacynar†; Cholagogum; Cynacur†; Hepacyn; Hepagallin N†; Hepar SL; Hepar-POS; Heparstad; Hewechol Artischockendragees†; Natu-Hepa; *Pol.*: Cynacholin; Cynarex; Digestiol; Hepacynar; Liproxal; *Rus.*: Chophytol (Хофитол); *Spain*: Cirkuhep; *Switz.*: Chophytol; Hepa-S; Legadyn; Natu-Hepa; *Turk.*: Digestor; *UK*: Cypar Artichoke; DigestAid; Digestherb; Phytocleanse; *Ukr.*: Artihol (Артихол); Bilicur (Билікур); Chophytol (Хофитол); Cynarix (Цинарикс).

Multi-ingredient Preparations. *Arg.*: Adelgazar; Alcachofa Plus; Arceligasol; Bagohepat; Bilidren; Boldina; Chofitol Plus; Digenat; Dioxicolagol; Fegalgina; HDG; Hepachofa; Hepacur; Hepatalgina; Hepatalgina; Hepatodirectol; Lorbihepatic†; Lorhepatic; Metiogen; Palatrobil; Palatrobil; Wunderbalsam; *Austral.*: Digest Aid; Extralife Liva-Care†; KickStart Detox; Liver Detox; Liver Tonic Complex; Livton Complex; PM Syrin; *Austria*: Cynarix comp; Gallesyn neu; Gallesyn neu; *Belg.*: Cynactil; *Braz.*: Chofraninа†; Colachofra; Figatil; Gotas Preciosas; Lisotox; Solvobil; *Canad.*: Artechol†; Articho-Nat; Duo-Bil; Gallexier†; Hepartichaut†; Hepartichaut; Hepaticol; Hepatol; Herbaraphanus†; Milk Thistle†; Phyto-Marinex; *Fr.*: Actibil†; Aromadetox†; Benetransit†; Biofirm; Canol; Elixir Spark†; Expuryl; Hepaclem†; Hepatoflorine†; *Ger.*: Carmol Magen-Galle-Darm†; Gallexier; Gallexier; *Hong Kong*: Hepatofalk†; Wellman†; *Hung.*: Gallexier; *Indon.*: Biocholes†; Hepagard; *Ital.*: Cinarepa; Colax†; *Mex.*: Bagohepat†; Chofabol; Hepedren; Ifuchol; *Philipp.*: Hepamin; *Pol.*: Cardiobonisol; Rapacholin AC†; Rapacholin C; Sylicynar; *Rus.*: Herbion Drops for the Gallbladder (Гербион Капли Желчегонные)†; *Singapore*: Vidaylin MiniBear; *Spain*: Cynaro Bilina†; Laxadinas†; Lipograsil†; Nico Hepatocyn; *Swed.*: Cynaramin; Galexir; *Switz.*: Bilifuge; Boldocynara; Kernosan 24; Strath Gouttes pour le foie et la bile; Tisane hepatique et biliaire; *UK*: Bio-Strath Artichoke Formula;

Digestisan; Milk Thistle Complex; Pure Plan; *Ukr.*: Choliver (Холивер)†; Detoxil (Детоксил); Ektis (Эктис); Farcovit B12 (Фарковит B12)†; Hepahealth (Гепахелс); Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); PM Sirin (ПМ Сирин); *Venez.*: Cynascool.

Homoeopathic Preparations. *Canad.*: Cynara Complex†; Formula FV 213; Formula Homeo QR 209†; Hecocur†; Hepar Compositum; *Chile*: Cynara Compuesta; Digherbal; *Fr.*: Homeogene 22†; *Ger.*: Hepar comp; Infihepan; *Neth.*: Apo-Hepat; Gletar; Hepeel H; *USA*: Preferred Remedies Detoxin.

Pharmacopoeial Preparations
Ph. Eur.: Artichoke Leaf Dry Extract.

Cynarine *(rINN)*

Cinarina; Cynarin; Cynarinum; Cynaryna; 1,5-Dicaffeoylquinic Acid; Цинарин.
1-Carboxy-4,5-dihydroxy-1,3-cyclohexylene bis(3,4-dihydroxycinnamate).
$C_{25}H_{24}O_{12}$=516.5
CAS — 1182-34-9; 1884-24-8.
UNII — 85D81U9JAV.

Profile

Cynarine is an active ingredient of cynara (p. 2490.3). It has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Cypress

Italian Cypress; Mediterranean Cypress.

Profile

Italian or Mediterranean cypress (*Cupressus sempervirens*, Cupressaceae) is included in preparations for peripheral vascular disorders.

It is the source of cypress oil. Cypress oil is used in preparations for the relief of cough and cold symptoms and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Arterase; Circulatonic†; Olioseptil Nez-Gorge; Veino Gomenol; Veinostase; *Ital.*: Colostrum; Venalta; *Spain*: Vapores Pyt†; *Switz.*: Eucapinol; Novital.

Cytidine

Cytosine Riboside; Цитидин.
4-Amino-1-β-D-ribofuranosyl-2-(1*H*)-pyrimidinone.
$C_9H_{13}N_3O_5$=243.2
CAS — 65-46-3.
UNII — 5CSZ8459RP.

Profile

Cytidine is an endogenous cytosine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Cytidine is used in preparations containing other nucleosides in the treatment of corneal damage. It has also been used in preparations for liver disorders, anaemias, and as a tonic. Disodium cytidine phosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; the triphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Kun Bang (坤邦).

Multi-ingredient Preparations. *Braz.*: Etna; Nucleo CMP; *Chile*: Citoneuron; *Ger.*: Keltican N†; *Hong Kong*: Vitacic†; *Ital.*: Centrum; *Mex.*: Nucleo CMP; *Mon.*: Vitacic; *Spain*: Nucleo CMP; *Ukr.*: Keltican (Кельтикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Cytisine

Baptitoxine; Laburnine; Sophorine; Ulexine; Цитизин.
1,2,3,4,5,6-Hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one.
$C_{11}H_{14}N_2O$=190.2
CAS — 485-35-8.
UNII — 53S5U404NU.

Profile

Cytisine is a highly toxic alkaloid found in laburnum (p. 2538.3) and some other leguminous plants. It resembles nicotine (p. 2569.3) in its actions and has been given orally as an aid to smoking cessation (p. 2570.2). The dose is 1.5 mg 6 times daily for 3 days which is then gradually reduced over the next 3 weeks to 1.5 mg twice daily for the final 5 days of treatment. Treatment of adverse effects of cytisine is as described for Nicotine, p. 2571.1.

A 0.15% solution of cytisine known as Cytitone has been used intravenously or intramuscularly in some countries as a respiratory stimulant.

References.

1. Etter J-F. Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 2006; 166: 1553–9.
2. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep* 2006; 58: 777–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Bulg.*: Tabex (Табекс); *Pol.*: Tabex; *Rus.*: Tabex (Табекс); *Ukr.*: Tabex (Табекс).

Multi-ingredient Preparations. *Rus.*: Theophedrinum-N (Теофедрин-Н).

Cytochrome C

Citocromo C; Цитохром С.

Pharmacopoeias. *Chin.* includes Cytochrome C Solution and preparations for injection.

Profile

Cytochrome C is a haemoprotein occurring in the body and involved in electron and hydrogen transport in biological oxidation processes. It has been given intravenously in various hypoxic conditions.

Cytochrome C is an ingredient of some eye drops used for the treatment of cataract but its actions, if any, are unclear.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Sai Tuo (赛托); *Ital.*: Citophase; *Jpn*: Cytorest†.

Multi-ingredient Preparations. *Gr.*: Collyre Vitaphakol; Suprin; *Rus.*: Oftan Catachrom (Офтан Катахром).

Cytokines

Citocinas; Citokinas; Citoquinas; Цитокины.

Profile

Cytokines are a group of endogenous soluble peptides produced by many different cell types in response to noxious stimuli. In contrast to peptide hormones, they tend to act locally. Cytokines affect expression of genes influencing changes at the cellular level and have a regulatory function, acting as growth factors in cellular differentiation and/or proliferation. Cytokines are also involved in host responses to disease such as infection or inflammation. Some cytokines induce inflammation whereas others have an anti-inflammatory action through inhibition of proinflammatory cytokines. Cytokines are classified by their biological activity rather than structure and most are pleiotropic (i.e. they are multifunctional). A large number of cytokines alter endothelial function affecting permeability and may also cause cellular damage or death. Some cytokines are involved in the pathophysiology of diseases, particularly immune, inflammatory, and infectious diseases; they may also be involved in the development of cardiovascular disease.

Cytokines that are used clinically include:

- granulocyte colony-stimulating factors such as filgrastim (p. 1151.3)
- granulocyte-macrophage colony-stimulating factors such as molgramostim (p. 1156.2)
- interferons (p. 989.2)
- some interleukins (p. 2533.3)
- oprelvekin (p. 1157.2), a platelet growth factor
- palifermin (p. 2579.1), a keratinocyte growth factor
- somatomedins (p. 1929.1)
- thrombopoietin (p. 1164.1)
- trafermin (p. 1725.1), a fibroblast growth factor
- tumour necrosis factor (p. 878.1)
- urogastrone (p. 1894.3), an epidermal growth factor

Anticytokine-based therapy may involve suppressing the action of single or related cytokines by specific soluble cytokine receptors, antagonists to the cytokine receptor, or antibodies against the cytokine. Alternatively, the synthesis of several unrelated cytokines may be suppressed by a single therapeutic agent. Fusion toxins in which protein sequences from cytokines or natural growth factors are combined with a bacterial toxin have also been produced to target specific cytokines.

References.

1. Xing Z, Wang J. Consideration of cytokines as therapeutics agents or targets. *Curr Pharm Des* 2000; 6: 599–611.
2. Schooltink H, Rose-John S. Cytokines as therapeutic drugs. *J Interferon Cytokine Res* 2002; 22: 505–16.
3. Andreakos ET, *et al.* Cytokines and anti-cytokine biologicals in autoimmunity: present and future. *Cytokine Growth Factor Rev* 2002; 13: 299–313.
4. Stevceva L. Cytokines and their antagonists as therapeutic agents. *Curr Med Chem* 2002; 9: 2201–7.
5. Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets* 2006; 7: 675–81.
6. Villar CC, *et al.* Therapeutic modulation of cytokines in chronic infectious diseases. *Curr Pharm Des* 2006; 12: 2329–48.
7. Feurino LW, *et al.* Current update of cytokines in pancreatic cancer: pathogenic mechanisms, clinical indication, and therapeutic values. *Cancer Invest* 2006; 24: 696–703.

Damiana

Hierba de la pastora; Itamo real; Turnera; Дамиана.
UNII — RQ2CFA7WWJ.

Profile

Damiana is the dried leaves and stem of *Turnera diffusa* var. *aphrodisiaca* (Turneraceae) and possibly other species of *Turnera*. Damiana is drunk as a tea, and is used in herbal medicine for a variety of indications. It has a reputation as an aphrodisiac, but there is no evidence for this.

Homoeopathy

Damiana has been used in homoeopathic medicines under the following names: Turnera diffusa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Malaysia*: Cefagil.

Multi-ingredient Preparations. *Arg.*: ADX; Vitalsex; *Austral.*: Enhance for Men; For Women Active Woman Formula†; Herbal Rest & Relax; Masculine Herbal Complex; Meno Support Plus; Mens Performance Multi; Mens Super Soy/Clover†; Nevaton; Olf†; The Blue One†; Tribulus & Epimedium Compound; *Canad.*: Libeeda for Men; Libeeda for Women; *Hong Kong*: Sessoforte†; *Indon.*: Instink†; Maxirex; Menolia†; Neo Hormoviton; Tripote†; Tristan†; *Ital.*: Argidam; Dam; Euroton; *Mex.*: Zumba; *Pol.*: Tripoten; *UK*: Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Regina Royal Concorde; Strength; Zotrim.

Homoeopathic Preparations. *Austria*: Cefagil; Erbiode-Starkungstropfen; Orgafem; *Canad.*: Goldenrod Combination†; *Fr.*: Amphosca Orchitine; Amphosca Ovarine; Selenium Complexe No 99; *Ger.*: Cefagil; Manuia; Testerell; Virilis-Gastreu S R41; *Hung.*: Cefagil; *Rus.*: Damiana-Plus (Дамиана-Плюс); *Ukr.*: Cefagil (Цефагил).

Danshen

Chinese Sage; Chinese Salvia; Chinesischer Salbei; Dan Shen; Red Sage; Redroot Sage; Red-rooted Sage; Rotwurzsalbei; Tan Shen; Tan-shen; Шалфей многокорневищный.
CAS — 79483-68-4 (danshen root extract).
UNII — 3VOZ2N8O39.

NOTE. Distinguish from Dang Shen, the root of *Codonopsis pilosula* (Campanulaceae). The name Tan Shen is also applied to the dried roots of the related species *Salvia bowleyana* and *S. przewalskii*. The term Red Sage has been used for both *Salvia officinalis* (Sage, p. 2608.3) and *Salvia miltiorrhiza* (Danshen).

Pharmacopoeias. In *Chin.* and *US*. *Eur.* (see p. vii) includes Salvia Miltiorrhiza Root and Rhizome. *Br.* includes a separate monograph for Processed Salvia Miltiorrhiza Rhizome and Root. *US* includes Powdered Chinese Salvia.

Ph. Eur. 8: (Salvia Miltiorrhiza Root and Rhizome; Salviae Miltiorrhizae Radix et Rhizoma). The dried, whole or fragmented rhizome and root of *Salvia miltiorrhiza*, collected in spring or autumn. It contains not less than 3.0% of salvianolic acid B, ($C_{36}H_{30}O_{16}$=718.6), and not less than 0.12% of tanshinone II_A, ($C_{19}H_{18}O_3$=294.4), calculated with reference to the dried drug.

BP 2014: (Processed Salvia Miltiorrhiza Rhizome and Root). Salvia Miltiorrhiza Rhizome and Root that has been processed. It is collected in spring or autumn, separated from soil, washed, softened, sliced longitudinally or transversely, and dried. It may be stir baked with wine. It contains not less than 0.04% of tanshinone II_A ($C_{19}H_{18}O_3$=294.4), not less than 0.17% of rosmarinic acid ($C_{18}H_{16}O_8$=360.3), and not less than 3.0% of salvianolic acid B ($C_{36}H_{36}O_{16}$=724.7), calculated with reference to the dried material. Protect from moisture.

USP 36: (Chinese Salvia). It consists of the dried roots and rhizomes of *Salvia miltiorrhiza*, collected in spring or autumn. It contains not less than 0.1% of tanshinone IIA; not less than 0.2% of total tanshinones, calculated as the sum of cryptotanshinone, tanshinone I, and tanshinone IIA; and not less than 3.0% of salvianolic acid B; calculated on the dried basis. Protect from light and moisture.

Uses and Administration

Danshen is the dried root and rhizome of *Salvia miltiorrhiza* (Lamiaceae). It is used in traditional Chinese medicine mainly for cardiovascular disorders including ischaemic heart disease, ischaemic stroke, and hyperlipidaemias.

A root extract containing methylenetanshinquinone and 1,2-dihydrotanshinquinone has been described.

References.

1. Zhou L, *et al.* Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *J Clin Pharmacol* 2005; **45**: 1345–59.
2. Cheng TO. Cardiovascular effects of danshen. *Int J Cardiol* 2007; **121**: 9–22.
3. Qiu F, *et al.* Effect of danshen extract on the activity of CYP3A4 in healthy volunteers. *Br J Clin Pharmacol* 2010; **69**: 656–62.

Interactions

For mention of a possible interaction between *warfarin* and Chinese herbal remedies including danshen, see Chinese Herbal Remedies, p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Bupleurum Complex†; Dan Shen Compound; *Indon.*: Procardio†; *Malaysia*: Elgucare; NeuroAid; *Singapore*: NeuroAid.

Dehydrocholic Acid *(BAN, rINN)*

Acide Déhydrocholique; Ácido dehidrocólico; Acidum Dehydrocholicum; Chologon; Dehidrocólico, ácido; Dehydrocholsyra; Dehydrokoolihappo; Triketocholanic Acid; Дегидрохолевая Кислота.

3,7,12-Trioxo-5β-cholan-24-oic acid.

$C_{24}H_{34}O_5$=402.5

CAS — 81-23-2 (dehydrocholic acid); 145-41-5 (sodium dehydrocholate).

UNII — NH5000009I.

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

USP 36: (Dehydrocholic Acid). A white, fluffy, odourless powder. Practically insoluble in water; soluble 1 in 100 of alcohol, 1 in 135 of acetic acid at 15 degrees, 1 in 130 of acetone at 15 degrees, 1 in 35 of chloroform, 1 in 2200 of ether at 15 degrees, 1 in 135 of ethyl acetate at 15 degrees, and 1 in 960 of benzene at 15 degrees; solutions in alcohol and in chloroform are usually slightly turbid; soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates.

Profile

Dehydrocholic acid is a semisynthetic bile acid (p. 2457.2) that is given for its hydrocholeretic properties, increasing the volume and water content of the bile without appreciably altering the content of bile acids. It has been used to improve biliary drainage and has also been given for the temporary relief of constipation. The usual oral dose is 250 to 500 mg three times daily after meals.

Dehydrocholic acid is contra-indicated in significant cholelithiasis, complete mechanical biliary obstruction, and in severe hepatic impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Dycholium; *USA*: Cholan-HMB; Decholin.

Multi-ingredient Preparations. *Arg.*: Arnol; Bagohepat; Bibol Leloup; Bil 13 Enzimatico; Bil 13; Bilagol Antigas; Carbogasol Digestivo; Digenorflat; Hepachofa; Hepatalgina; Lorbihepatic†; Lorhepatic; Pakinase; Palatrobil; Pankreon Total; Zimerol; *Braz.*: B-Vesil†; Essen; Plasil Enzimatico; Sintozima†; *Canad.*: Hepartichaut†; Hepartichaut; Regubil; *Hung.*: Neo-Bilagit; *Mex.*: Bagohepat†; Plasil Enzimatico; *Philipp.*: Spasmo-Canulase; *Pol.*: Rapacholin C; Rapacholin Forte; *Port.*: Espasmo Canulase†; *S.Afr.*: Spasmo-Canulase†; *Spain*: Nulacin Fermentos†; *Switz.*: Spasmo-Canulase; *Thai.*: Vitana-EZ; Vitaral.

Pharmacopoeial Preparations

USP 36: Dehydrocholic Acid Tablets.

Delmopinol Hydrochloride *(rINNM)*

Delmopinol, Chlorhydrate de; Delmopinoli Hydrochloridum; Hidrocloruro de delmopinol; M-1650; Дельмопинола Гидрохлорид.

±-3-(4-Propylheptyl)-4-morpholineethanol hydrochloride.

$C_{16}H_{33}NO_3$,HCl=307.9

CAS — 79874-76-3 (delmopinol); 98092-92-3 (delmopinol hydrochloride).

Profile

Delmopinol prevents the formation of dental plaque by coating the teeth and preventing adhesion of bacteria. The hydrochloride is used as a mouth rinse in the treatment and prevention of gingivitis.

References.

1. Addy M, *et al.* Meta-analyses of studies of 0.2% delmopinol mouth rinse as an adjunct to gingival health and plaque control measures. *J Clin Periodontol* 2007; **34**: 58–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Auxinol; *Israel*: Decapinol; *UK*: Decapinol.

Demelverine Hydrochloride *(rINNM)*

Démelvérine, Chlorhydrate de; Demelverini Hydrochloridum; Hidrocloruro de demelverina; Methphenaethamine Hydrochloride; *N*-Methyldiphenethylamine Hydrochloride; Демельверина Гидрохлорид.

N-Methyl-*N*-(2-phenylethyl)-benzeneethanamine hydrochloride.

$C_{17}H_{21}N$,HCl=275.8

CAS — 13977-33-8 (demelverine); 18719-09-0 (demelverine hydrochloride).

UNII — T568N7L7GE.

Profile

Demelverine hydrochloride is an antispasmodic that has been used in the treatment of smooth muscle spasm.

Deoxyribonucleic Acid

ADN; Animal Nucleic Acid; Desoxirribonucleico, ácido; Desoxypentose Nucleic Acid; Desoxyribonucleic Acid; Desoxyribose Nucleic Acid; DNA; Thymus Nucleic Acid; ДНК; Дезоксирибонуклеиновая Кислота.

UNII — 8JCB80Q5K1.

Profile

Deoxyribonucleic acid (DNA) is a nucleic acid (p. 2573.1) in which the pentose sugar moiety of the nucleotides is deoxyribose, the purine bases are adenine (p. 2430.2) and guanine, and the pyrimidine bases are cytosine and thymine. Hydrogen bonds between complementary pairs of purine and pyrimidine bases link 2 polynucleotide strands, which are twisted to form a double helix with the bases on the inside of the structure and the sugar-phosphate backbone on the outside. Pairing of bases between complementary strands of DNA is always the same: adenine with thymine and cytosine with guanine. DNA is present in cell nuclei and its function is to carry the genetic material of cellular organisms and DNA viruses. It also provides the template for the production of ribonucleic acid (p. 2604.1). For the role of DNA in gene therapy, see p. 2511.2.

Proprietary preparations of DNA are marketed in some countries for a variety of debilitating and convalescent conditions; the sodium and magnesium salts of DNA have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: ADN†; *Ital.*: Placentex; *Rus.*: Derinat (Дериват).

Multi-ingredient Preparations. *Arg.*: RNA DNA; *Fr.*: Osteogen†; *India*: Placentrex.

Dextran Sulfate *(BANM, rINNM)*

Dextran, Sulfate de; Dextran Sulfate Sodium; Dextran Sulphate; Dextran Sulphate Sodium; Dextrani Sulfas; Dextrano, sulfato de; Sulfato de dextran; Декстрана Сульфат.

CAS — 9011-18-1.

ATC — B05AA05.

ATC Vet — QB05AA05.

Pharmacopoeias. In *Jpn*.

Profile

Dextran sulfate is the sodium salt of sulfuric acid esters of dextran. It has been used as an anticoagulant and as a lipid regulating drug, and has been investigated for its antiviral activity. Dextran sulfate potassium has also been used.

Interactions. As mentioned on p. 1287.1 (under Hypersensitivity), anaphylactoid reactions have occurred in patients receiving ACE inhibitors during low-density lipoprotein apheresis using a dextran sulfate-cellulose column.[1,2] Withdrawal of the ACE inhibitor for 1 to 3 days before apheresis may prevent the reaction.[2]

1. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340**: 908–9.
2. Agishi T. Anion-blood contact reaction (ABC reaction) in patients treated by LDL apheresis with dextran sulfate-cellulose column while receiving ACE inhibitors. *JAMA* 1994; **271**: 195–6.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Diroseal; *Chile*: Cicapost; Diroseal; Ureadin Rx DB; *Fr.*: Avene Antirougeurs; Creme au Melilot Composee†; Dextrarine Phenylbutazone; Diroseal†; *Hung.*: Doxivenil†; *Ital.*: Stranoval; *Port.*: Cicapost; *Switz.*: Doxivenil†; *Venez.*: Doxivenil.

Dextrorphan *(BAN, pINN)*

Dextrorfano; Dextrorphane; Dextrorphanum; Ro-1-6794; Декстрорфан.

17-Methyl-9α,13α,14α-morphinan-3-ol.

$C_{17}H_{23}NO$=257.4

CAS — 125-73-5.

UNII — 04B7QNO9WS.

Dextrorphan Hydrochloride *(BANM, USAN, pINNM)*

Dextrorfano, hidrocloruro de; Dextrorphane, Chlorhydrate de; Dextrorphani Hydrochloridum; Hidrocloruro de dextrorfano; Ro-01-6794/706; Декстрорфана Гидрохлорид.

$C_{17}H_{23}NO$,HCl=293.8

CAS — 69376-27-8.

Profile

Dextrorphan, a metabolite of dextromethorphan (p. 1660.1), is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It possesses some cough suppressant activity and has been investigated as a neuroprotective agent in the management of stroke.

References.

1. Albers GW, *et al.* Safety, tolerability, and pharmacokinetics of the N-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. *Stroke* 1995; **26**: 254–8.

Dichlorodiethylsulfide

Dichlorodiethylsulphide; Gas mostaza; Iperita; Mustard Gas; Sulfur Mustard; Sulfuro de dicloroetileno; Yellow Cross Liquid; Yperite.

Bis(2-chloroethyl)sulphide.

$C_4H_8Cl_2S$=159.1

CAS — 505-60-2.

UNII — T8KEC9FH9P.

Profile

Dichlorodiethylsulfide was developed for use in chemical warfare and has even more severe vesicant and irritant properties than its nitrogen analogue, chlormethine (p. 765.2). It was formerly used topically in the treatment of psoriasis.

Reviews of the toxicology of dichlorodiethylsulfide,[1-4] and debate on the management of casualties injured by dichlorodiethylsulfide and other chemical warfare agents.[5-11] Most patients exposed to dichlorodiethylsulfide recover largely or completely and only a small proportion will have severe long-term eye or lung damage,[12,13] although death from respiratory, renal, and bone-marrow

failure may occur.[11] A combination of 1% phenol and 1% menthol applied topically produced significant relief of pruritus compared with placebo in a randomised study of 80 war veterans with chronic skin lesions after exposure to dichlorodiethylsulfide.[14]

Eleven fishermen who accidentally retrieved corroded and leaking gas shells containing dichlorodiethylsulfide from underwater dumps, presented with very inflamed skin, especially in the axillary and genitofemoral regions, yellow blisters on the hands and legs, painful irritation of the eyes, and transient blindness. Two developed pulmonary oedema.[15] There was evidence of a mutagenic effect and in view of the increased risk of lung cancer in soldiers and workers exposed to the gas it is reasonable to assume that fishermen heavily exposed to dichlorodiethylsulfide also have an increased cancer risk.

1. Smith KJ, *et al.* Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. *J Am Acad Dermatol* 1995; 32: 765–76.
2. Dacre JC, Goldman M. Toxicology and pharmacology of the chemical warfare agent sulfur mustard. *Pharmacol Rev* 1996; 48: 289–326.
3. Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology* 2005; 214: 198–209.
4. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. *Fundam Clin Pharmacol* 2005; 19: 297–315.
5. Heyndrickx-A, Heyndrickx B. Management of war gas injuries. *Lancet* 1990; ii: 1248–9.
6. Fouyn T, *et al.* Management of chemical warfare injuries. *Lancet* 1991; 337: 121.
7. Willems JL, *et al.* Management of chemical warfare injuries. *Lancet* 1991; 337: 121–2.
8. Maynard RL, *et al.* Management of chemical warfare injuries. *Lancet* 1991; 337: 122.
9. Newman-Taylor AJ, Morris AJR. Experience with mustard gas casualties. *Lancet* 1991; 337: 242.
10. Heyndrickx A. Chemical warfare injuries. *Lancet* 1991; 337: 430.
11. Rees J, *et al.* Mustard gas casualties. *Lancet* 1991; 337: 430.
12. Murray VSG, Volans GN. Management of injuries due to chemical weapons. *BMJ* 1991; 302: 129–30.
13. Khateri S, *et al.* Incidence of lung, eye, and skin lesions as late complications in 34 000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003; 45: 1136–43.
14. Panahi Y, *et al.* Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Med J* 2007; 48: 392–5.
15. Wulf HC, *et al.* Sister chromatid exchanges in fishermen exposed to leaking mustard gas shells. *Lancet* 1985; i: 690–1.

Digitalin

Amorphous Digitalin; Digitalina; Digitalinum Purum Germanicum.

UNII — Q15ECE254B.

NOTE. Distinguish from Digitaline Cristallisée (digitoxin, p. 1353.1) which is very much more potent.

Profile

Digitalin is a standardised mixture of glycosides from *Digitalis purpurea*. It has actions similar to those of digoxin (p. 1353.3). Because of its ready solubility in water it was formerly used for the preparation of solutions for injection. It is also present in some ophthalmic preparations.

Dihydroxydibutylether

Dihidroxidibutiléter; Hydroxybutyloxide.

4,4′-Oxybis(butan-2-ol).

$C_8H_{18}O_3$=162.2

CAS — 821-33-0.

Profile

Dihydroxydibutylether is a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Dyskinebyl (保丹健素).

Multi-ingredient Preparations. *Arg.*: Binvex; *Ital.*: Dis-Cinil Complex.

Dill

Aneth; Anethum; Eneldo; Укроп.

UNII — Y05PC43ZRH.

NOTE. Indian Dill is the dried ripe fruits of *Anethum sowa*.

Pharmacopoeias. *Br.* includes Anethum Graveolens Sowa Fruit. *Fr.* includes dill fruit.

BP 2014: (Anethum Graveolens Sowa Fruit). The dried ripe fruit of *Anethum graveolens*. It contains not less than 0.3% of essential oil calculated with reference to the anhydrous drug.

Profile

Dill (*Anethum graveolens*, Apiaceae) is a culinary herb and has also been used in herbal medicine. It is the source of dill oil (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Colax†; Colax; *Hung.*: Lactonic.

Homoeopathic Preparations. *Canad.*: Lemon Balm†; *Fr.*: Billerol.

Dill Oil

Aceite esencial de aneto; Aceite esencial de hinojo hediondo; Aceite esencial del falso anis; Eneldo, aceite esencial de; European Dill Seed Oil; Oleum Anethi; Укропное Масло.

CAS — 8016-06-6.

UNII — 86T27UW55G.

Pharmacopoeias. In *Br.*

BP 2014: (Dill Oil). A clear colourless or pale yellow liquid, visibly free from water, obtained by distillation from the dried ripe fruits of *Anethum graveolens*. It darkens with age and has a characteristic odour of the crushed fruit. It contains 43 to 63% of carvone. At 20 degrees, soluble 1 in 1 or more of alcohol (90%) and 1 in 10 or more of alcohol (80%). Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

Profile

Dill oil, usually in the form of dill water, is used as an aromatic carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p. 1807.1). It has also been used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Woodwards Gripe Water; *Fr.*: Aromadetox†; Aromadigest†; Aromazen†; *Hong Kong*: Infant-Sed†; *Hung.*: Woodward's Gripe Water; *India*: Bestozyme P; Bestozyme; Betip; Carmicide DPS; Colicaid; Coliky; Coliza; Cymbi; Decolic Infant; DP-Spas DPS; Gastica; Merispas; Merozyme-C; Neopeptine; Panoric; *Israel*: Dentinox; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water; *Malaysia*: Bonnisan; *Rus.*: Solutan (Солутан)†; *Singapore*: Dentinox Colic Drops; *Thai.*: Baby Gripe†; Bebidol; Gripe Mixture; Woodwards Gripe Water†; *UK*: Atkinson & Barker's Gripe Mixture; Neo Baby Gripe Mixture; Neo Gripe Mixture; Nurse Harvey's Gripe Mixture; Woodwards Gripe Water.

Dimecrotic Acid *(rINN)*

Acide Dimécrotique; Ácido dimecrótico; Acidum Dimecroticum; Димекротовая Кислота.

2,4-Dimethoxy-β-methylcinnamic acid.

$C_{12}H_{14}O_4$=222.2

CAS — 7706-67-4.

UNII — R46Y1C0ZR2.

Profile

Dimecrotic acid has been used as the magnesium salt as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Hepadial; *Port.*: Hepadoddi; Hepaquifa†; *Spain*: Fisiobil.

Dimethoxymethane

Dimethoximethane; Dimetoximetano; Formal; Formaldehído dimetilacetal; Formaldehyde Dimethyl Acetal; Methylal; Metilal; Метиналь; Диметоксиметан.

$CH_2(OCH_3)_2$=76.10

CAS — 109-87-5.

UNII — 7H1M4G2NUE.

Profile

Dimethoxymethane has been used in perfumery. It has been included in preparations for topical analgesia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: PR Freeze Spray.

Dimethyl Sulfone

Dimethyl Sulphone; Dimetylosulfon; $DMSO_2$; Methyl Sulphone; Methylsulfonylmethane; Methylsulphonylmethane; MSM; Sulfonylbismethane; Диметилсульфон.

$C_2H_6O_2S$=94.13

CAS — 67-71-0.

UNII — 9H4PO4Z4FT.

Pharmacopoeias. In *US*.

USP 36: (Methylsulfonylmethane). A white powder or flake crystal. Freely soluble in water, in alcohol, in acetone, and in methyl alcohol; sparingly soluble in ether.

Profile

Dimethyl sulfone is an oxidation product of dimethyl sulfoxide (p. 2182.2) and has been used similarly as an organic solvent. It may be responsible for some of the pharmacological actions of dimethyl sulfoxide and has been tried in disorders including osteoarthritis, allergic rhinitis, and interstitial cystitis. It has also been used as a nutritional supplement.

References.

1. Ely A, Lockwood B. What is the evidence for the safety and efficacy of dimethyl sulfoxide and methylsulfonylmethane in pain relief? *Pharm J* 2002; 269: 685–7.
2. Anonymous. Methylsulfonylmethane (MSM). *Altern Med Rev* 2003; 8: 438–41.
3. Brien S, *et al.* Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 200816: 1277–88.

Musculoskeletal and joint disorders. An evidence-based report[1] into the use of complementary medicines to treat rheumatic diseases concluded that dimethyl sulfone may have a moderate effect in improving symptoms of osteoarthritis, although the evidence is limited and from short-term studies.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Arg.*: Glucometil 3; Glucometil K Duo; *Austral.*: Joint Formula Advanced with MSM Booster; Osteo-Relief Plus MSM; OsteoEze Active + MSM; *Fr.*: Rhumadol; *India*: Altocerin-GM; Baknil; Bonjo Aid; Cartigen Plus; Cartivit; Cartiwel; Cartizole Plus; Compensate; Conjoint; Cool-Joint; DN Plus; Fremov-ME; Fremov; Joint Guard; Jointace-DN; Jointop; Jonty; Mecocas-Ortho; Mobijoint; Necare; Nurokind Ortho; OA Plus; Orbone; Orthocerin-G; Osicare; Ostawin; Osteojoin-D; Ostiwel Forte; Paclo-GMD; *Indon.*: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Bonic Plus; Cartiflex; GCM; Joint Care Plus; Jointace; Maxitrin†; OA Plus; Ositin; Osteoflam; Osteokom Forte; Osteokom; Osteor Plus; Ostrimix; Osvion Plus; Rebone; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viostin-X; *Israel*: Mega Gluflex with MSN; *Ital.*: Artrosulfur; Broncosulfur; Condrorexil; Neosulfur†; Osteoclar; Osteolip Crema; Reumafort; Rino Get; *Mex.*: Mex-Amina; *Philipp.*: Lungcaire Plus; Osteoaid; *Port.*: Synchrorose Intensivo; *S.Afr.*: ProFLEX 750†; *UK*: GlucOsamax; NatraFlex; PainEaze; *Ukr.*: Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; *USA*: Stopain Cold Extra Strength.

Pharmacopoeial Preparations

USP 36: Glucosamine and Methylsulfonylmethane Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets; Methylsulfonylmethane Tablets.

p,α-Dimethylbenzyl Alcohol

Tolinol; *p*-Tolylmethylcarbinol; Tolynolum.

1-(*p*-Tolyl)ethanol.

$C_9H_{12}O$=136.2

CAS — 536-50-5.

NOTE. The name tolynol has been applied to both *p*,α-dimethylbenzyl alcohol and mephenesin (p. 2025.2).

Profile

p,α-Dimethylbenzyl alcohol has been used as a choleretic in the treatment of hepatic disorders and is an ingredient of preparations for gastrointestinal disorders. *p*,α-Dimethylbenzyl alcohol nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Apozema†; Galle-Donau; Spasmo Claim†; *China*: Galle-Donau (加诺).

Dimethyltryptamine

Dimetiltriptamina; DMT; *N,N*-Dimethyltryptamine.
3-(2-Dimethylaminoethyl)indole.
$C_{12}H_{16}N_2$=188.3
CAS — 61-50-7.
UNII — WUB601BHAA.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dimethyltryptamine:

45 Minute Psychosis; 45 Minute Trip; AMT; Businessman's LSD; Businessman's special; Businessman's trip; DET; Disneyland; Disneyworld; Dmitri; DMT; Fantasia; Instant psychosis; Psychosis.

Profile

Dimethyltryptamine is an active principle obtained from the seeds and leaves of *Piptadenia peregrina* (Mimosaceae) from which the hallucinogenic snuff cohoba is prepared. It may also be obtained from other South American plants. It has been reported to be present in the tropical legume *Mucuna pruriens*.

Dimethyltryptamine produces hallucinogenic and sympathomimetic effects that are similar to those of lysergide (p. 2547.1), but of shorter duration. It has no therapeutic use. Related synthetic hallucinogens subject to abuse include:

- diethyltryptamine (DET)
- dipropyltryptamine (DPT)
- 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT; Foxy; Foxy Methoxy; Methoxy Foxy)

References.
1. Alatrash G, *et al.* Rhabdomyolysis after ingestion of "foxy," a hallucinogenic tryptamine derivative. *Mayo Clin Proc* 2006; 81: 550–1.

Dimevamide (rINN)

Aminopentamide; Dimevamida; Dimévamide; Dimevamidum; Диметамид.
α-[2-(Dimethylamino)propyl]-α-phenylbenzeneacetamide.
$C_{19}H_{24}N_2O$=296.4
CAS — 60-46-8.
UNII — IP1847L61M.

Dimevamide Sulfate (rINNM)

Aminopentamide Sulfate; Dimevamida, sulfato de; Diméva-mide, Sulfate de; Dimevamidi Sulfas; Sulfato de dimevamida; Диметамида Сульфат.
$C_{19}H_{24}N_2O.H_2SO_4$=394.5
CAS — 35144-63-9 (xH_2SO_4).
UNII — 20P9NI883O.

Pharmacopoeias. In *US* for veterinary use only.

Profile

Dimevamide is a tertiary amine and has been used as an antimuscarinic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Kantrexil.

2,4-Dinitrochlorobenzene

2,4-Dinitroclorobenceno; DNCB; 2,4-Динитрохлорбензол.
1-Chloro-2,4-dinitrobenzene.
$C_6H_3ClN_2O_4$=202.6
CAS — 97-00-7.

Profile

2,4-Dinitrochlorobenzene is a potent sensitiser that has been applied topically in the evaluation of delayed hypersensitivity. It has also been used as an immunostimulant in various conditions including some forms of cancer, and in the treatment of alopecia and warts. It has also been investigated in HIV infection and leprosy.

2,4-Dinitrochlorobenzene has been reported to be mutagenic *in vitro*.

References.
1. Happle R. The potential hazards of dinitrochlorobenzene. *Arch Dermatol* 1985; 121: 330–2.
2. Todd DJ. Topical treatment with dinitrochlorobenzene. *Lancet* 1995; 346: 975.
3. Stricker RB, Goldberg B. Safety of topical dinitrochlorobenzene. *Lancet* 1995; 346: 1293.
4. Strobbe LJ, *et al.* Topical dinitrochlorobenzene combined with systemic dacarbazine in the treatment of recurrent melanoma. *Melanoma Res* 1997; 7: 507–12.
5. Yoshizawa Y, *et al.* Successful immunotherapy of chronic nodular prurigo with topical dinitrochlorobenzene. *Br J Dermatol* 1999; 141: 387–9.
6. Yoshizawa Y, *et al.* Topical dinitrochlorobenzene therapy in the treatment of refractory atopic dermatitis: systemic immunotherapy. *J Am Acad Dermatol* 2000; 42: 258–62.
7. Yoshizawa Y, *et al.* Systemic immunotherapy with topical dinitrochlorobenzene as additional treatment of alopecia areata. *Acta Derm Venereol* 2002; 82: 136–8.
8. von Nida J, Quirk C. Successful treatment of in-transit melanoma metastases using topical 2-4 dinitrochlorobenzene. *Australas J Dermatol* 2003; 44: 277–80.

Dioxins

NOTE. The name Dioxin has also been applied to dimethoxane.

Profile

The term 'dioxins' encompasses a large group of closely related chemicals known as polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). The most toxic is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

Dioxins are byproducts in the manufacture of commercial chemical products such as chlorinated phenols and polychlorinated biphenyls (PCBs), and can also be produced in smaller quantities by combustion processes and industrial waste. They first came to public attention during the Vietnam war, when they were found to be present in the herbicide Agent Orange used as a defoliant. They are incriminated as causing chloracne (a severe and persistent acne caused by chlorinated compounds). They are potent teratogens and carcinogens in *animals*. An increased incidence of cancer at different organs due to dioxins has been claimed but this has not been substantiated by clinical and follow-up studies. An effect on cell-mediated immunity has been noted.

Exposure should be limited to the lowest feasible concentration.

Adverse effects. The impact of dioxins in food and the environment has been reviewed.[1-4]

An excess of soft tissue sarcomas was found in workers exposed to chlorophenoxy herbicides including those contaminated with TCDD,[5] but cautious interpretation of these results was advised.[6] In Vietnam veterans the risk of non-Hodgkin's lymphoma was about 50% higher than control subjects, but was not related to exposure to Agent Orange, nor was there evidence for an increase in other cancers.[7] Exposure to TCDD was implicated in an increase in cancer mortality in chemical workers,[8,9] but confounding factors such as smoking may have been present.[9,10] Other studies[11,12] have not shown an association between dioxin exposure and an increase in the incidence of human cancer, and epidemiological studies after occupational or accidental exposures have found no clear persistent systemic effects, except for chloracne, and no clear association with carcinogenesis or reproductive disorders.[1,2] Decreased plasma immunoglobulin G concentrations were measured in people after exposure to TCDD 20 years earlier as a result of accidental environmental contamination in Seveso, Italy.[13] A statistically significant increase in the incidence of breast cancer related to serum levels of TCDD was seen in a cohort of 981 women who ranged in age from infancy to 40 years in 1976 at the time of the Seveso accident.[14] The authors pointed out that this cohort is relatively young and continued follow-up would clarify any possible pathogenic role of TCDD.

In the USA, the National Academy of Sciences' Institute of Medicine is reported to have carried out an evaluation of publications on herbicide exposure, largely in industrial and agricultural workers.[15] They concluded that exposure to herbicides or dioxin was associated with soft-tissue sarcomas, Hodgkin's disease, non-Hodgkin lymphoma, chloracne, and porphyria cutanea tarda, and that there was limited evidence of an association with respiratory and prostate cancers and multiple myeloma. An update to the report has also suggested a link between Agent Orange exposure and spina bifida in veterans' offspring.[16] There is some evidence that exposure of men to TCDD is associated with a decreased male to female sex ratio in their offspring.[17] Results from studies[18-20] suggest that prenatal exposure to PCBs has an effect on mental and motor development in early childhood, although this may be counteracted by an advantageous home environment. However, virtually no adverse effects in relation to postnatal exposure to PCBs present in breast milk were shown.[20]

1. Food Standards Agency UK. Dioxins and PCBs in the UK diet: 1997 Total Diet Study (Number 04/00) (issued September 2000). Available at: http://www.food.gov.uk/science/surveillance/fsis2000/4diox (accessed 24/07/08)
2. DEFRA. Dioxins and dioxin-like PCBs in the UK environment (issued October 2002). Available at: http://www.scotland.gov.uk/Resource/Doc/1052/0002248.pdf (accessed 24/07/08)
3. WHO. Dioxins and their effects on human health (issued November 2007). Available at: http://www.who.int/mediacentre/factsheets/fs225/en/print.html (accessed 24/07/08)
4. FAO. Dioxins in the food chain: prevention and control of contamination (issued April 2008). Available at: http://www.fao.org/ag/agn/agns/files/Dioxin_fact%20sheet.pdf (accessed 24/07/08)
5. Saracci R, *et al.* Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; 338: 1027–32.
6. Petro R. Occupational exposure to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991; 338: 1392.
7. Suskind R. The association of selected cancers with service in the US military in Vietnam. *Arch Intern Med* 1990; 150: 2449–50.
8. Manz A, *et al.* Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 1991; 338: 959–64.
9. Fingerhut MA, *et al.* Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991; 324: 212–18.
10. Triebig G. Is dioxin carcinogenic? *Lancet* 1991; 338: 1592.
11. Coggon O, *et al.* Mortality and incidence of cancer at four factories making phenoxy herbicides. *Br J Ind Med* 1991; 48: 173–8.
12. Green LM. A cohort mortality study of forestry workers exposed to phenoxy acid herbicides. *Br J Ind Med* 1991; 48: 234–8.
13. Baccarelli A, *et al.* Immunologic effects of dioxin: new results from Seveso and comparison with other studies. *Environ Health Perspect* 2002; 110: 1169–73.
14. Warner M, *et al.* Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* 2002; 110: 625–8.
15. McCarthy M. Agent Orange. *Lancet* 1993; 342: 362.
16. Stephenson J. New IOM report links Agent Orange Exposure to risk of birth defect in Vietnam vets' children. *JAMA* 1996; 275: 1066–7.
17. Mocarelli P, *et al.* Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000; 355: 1858–63.
18. Walkowiak J, *et al.* Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet* 2001; 358: 1602–7.
19. Vreugdenhil HJ, *et al.* Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. *J Pediatr* 2002; 140: 48–56.
20. Jacobson JL, Jacobson SW. Association of prenatal exposure to an environmental contaminant with intellectual function in childhood. *J Toxicol Clin Toxicol* 2002; 40: 467–75.

Diphemanil Metilsulfate (BAN, rINN)

Difemanilo, metilsulfato de; Diphemanil Methylsulfate; Diphemanil Methylsulphate; Diphémanil, Métilsulfate de; Diphemanili Metilsulfas; Diphenmethanil Methylsulphate; Metilsulfato de difemanilo; Vagophemanil Methylsulphate; Дифеманила Метилсульфат.
4-Benzhydrylidene-1,1-dimethylpiperidinium methylsulphate.
$C_{20}H_{24}N.CH_3SO_4$=389.5
CAS — 62-97-5.
ATC — A03AB15.
ATC Vet — QA03AB15.
UNII — W2ZG23MGYL.

Profile

Diphemanil metilsulfate is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). It has been used topically as a 2% cream or powder to treat hyperhidrosis (p. 1685.1).

Diphemanil metilsulfate, given orally, has been used for the treatment of symptomatic bradycardia in infants.

References.
1. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in healthy subjects. *Eur J Clin Pharmacol* 1992; 42: 689–91.
2. Vidal AM, *et al.* Pharmacokinetics of diphemanil methylsulphate in infants. *Eur J Clin Pharmacol* 1993; 45: 89–91.
3. Pariente-Khayat A, *et al.* Pharmacokinetics of diphemanil methylsulphate in neonates and in premature infants. *Eur J Clin Pharmacol* 1996; 50: 429–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Prantal; *NZ*: Prantal†.

Diphenyl

Bifenilo; Difenilo; E230; Fenilbenceno; Phenylbenzene; Дифенил.
Biphenyl.
$C_{12}H_{10}$=154.2
CAS — 92-52-4.
UNII — 2L9GJK6MGN.

Profile

Diphenyl is fungistatic against a limited number of moulds and has been employed for impregnating the material used for wrapping citrus fruits.

Adverse effects. Workers exposed to high concentrations of diphenyl (up to 128 mg/m³) developed toxic symptoms that included irritation of the throat and eyes, headache, nausea, diffuse abdominal pain, numbness, aching of limbs, and general fatigue.[1] One of the workers, who also had somnolence, icterus, ascites, and oedema of the legs,

died; at autopsy, the liver showed necrosis. Chronic hepatitis was reported in a woman exposed over a 25-year period to diphenyl in the paper used to pack citrus fruit.[2] There has also been a report[3] of a small cluster of cases of parkinsonism associated with diphenyl exposure.

1. Häkkinen I, *et al.* Diphenyl poisoning in fruit paper production. *Arch Environ Health* 1973; 26: 70–4.
2. Carella G, Bettolo PM. Reversible hepatotoxic effects of diphenyl: report of a case and a review of the literature. *J Occup Med* 1994; 36: 575–6.
3. Wastensson G, *et al.* Parkinson's disease in diphenyl-exposed workers—a causal association? *Parkinsonism Relat Disord* 2006; 12: 29–34.

Dipivefrine *(BAN, rINN)* ⊗

Dipivalyl; Epinephrine; Dipivefriini; Dipivefrin (USAN); Dipivefrina; Dipivéfrine; Dipivefrinum; DPE; Дипивефрин.

$C_{19}H_{29}NO_5$=351.4

CAS — 52365-63-6.

ATC — S01EA02.

ATC Vet — QS01EA02.

UNII — 8Q1PVL543G.

Dipivefrine Hydrochloride *(BANM, rINNM)* ⊗

Dipivalyl Adrenaline Hydrochloride; Dipivalyl Epinephrine Hydrochloride; Dipivefrininhydrokloridi; Dipivefrin Hydrochloride; Dipivefrina, hidrocloruro de; Dipivéfrine, chlorhydrate de; Dipivefrinhydrochlorid; Dipivefrin-hydrochlorid; Dipivefrinhydroklorid; Dipivefrini Hydrochloridum; Dipivefrino hidrochloridas; Dipiwefryny chlorowodorek; Hidrocloruro de dipivefrina; Дипивефрина Гидрохлорид.

(*RS*)-4-[1-Hydroxy-2-(methylamino)ethyl]-o-phenylene dipivalate hydrochloride.

$C_{19}H_{29}NO_5.HCl$=387.9

CAS — 64019-93-8.

ATC — S01EA02.

ATC Vet — QS01EA02.

UNII — 5QTH9UHV0K.

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

Ph. Eur. 8: (Dipivefrine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane; very soluble in methyl alcohol.

USP 36: (Dipivefrin Hydrochloride). White, crystalline powder or small crystals, having a faint odour. Very soluble in water. Store in airtight containers.

Profile

Dipivefrine is an ester and prodrug of adrenaline (p. 1292.1). A 0.1% solution of the hydrochloride is used topically as eye drops to reduce intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (p. 1999.1).

References.

1. Parrow KA, *et al.* Is it worthwhile to add dipivefrin HCl 0.1% to topical β_1-, β_2-blocker therapy? *Ophthalmology* 1989; 96: 1338–41.
2. Drake MV, *et al.* Levobunolol compared to dipivefrin in African American patients with open angle glaucoma. *J Ocul Pharmacol* 1993; 9: 91–5. Correction. *ibid.*: 385.
3. Albracht DC, *et al.* A double-masked comparison of betaxolol and dipivefrin for the treatment of increased intraocular pressure. *Am J Ophthalmol* 1993; 116: 307–13.
4. Widengard I, *et al.* Effects of latanoprost and dipivefrin, alone or combined, on intraocular pressure and on blood-aqueous barrier permeability. *Br J Ophthalmol* 1998; 82: 404–6.
5. Vilaplana J, *et al.* Contact dermatitis by dipivefrine. *Contact Dermatitis* 2005; 52: 169–70.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipivefrine 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 31/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dipoquin†; Propine†; *Belg.*: Propine†; *Braz.*: Propine; *Canad.*: Propiné†; *Denm.*: Propine†; *Fin.*: Propine†; *Fr.*: Propine†; *Ger.*: d Epifrin†; Glaucothil†; *Gr.*: Diopine; Glaucodose; Pivefrin; Prodren; Thilodrin; *Hong Kong*: Propine†; *Irl.*: Propine†; *Israel*: Difrin†; *Ital.*: Propine; *Jpn*: Pivalephrine; *Neth.*: Diopine†; *Norw.*: Propine†; *NZ*: Propine†; *Singapore*: Propine†; *Spain*: Diopine†; *Swed.*: Propine†; *Thai.*: Propine; *UK*: Propine†; *USA*: AkPro†; Propine.

Multi-ingredient Preparations. *Austria*: Thiloadren†; *Canad.*: Probeta†; *Ger.*: Thilodigon†; *Gr.*: Ryvina; Thilocombin; Thilodigon.

Pharmacopoeial Preparations

BP 2014: Dipivefrine Eye Drops;

USP 36: Dipivefrin Hydrochloride Ophthalmic Solution.

Diquafosol Tetrasodium *(BANM, USAN, rINNM)*

Diquafosol tetrasódico; Diquafosol tetrasodique; Diquafosolum tetranatricum; INS-365; Диквафозол Тетранатрий.

Uridine(5′)tetraphospho(5′)uridine tetrasodium.

$C_{18}H_{22}N_4Na_4O_{25}P_4$=878.2

CAS — 211427-08-6.

UNII — X8T95BH9LL.

NOTE. The code KPY-998 has been variously applied to diquafosol and to diquafosol tetrasodium. The name Prolacria has been used as a trade mark for diquafosol tetrasodium.

Profile

Diquafosol is a $P2Y_2$-receptor agonist and has mucolytic properties. It is used as the tetrasodium salt in the management of dry eyes and has also been studied in respiratory disorders including cystic fibrosis.

References.

1. Nichols KK, *et al.* Diquafosol tetrasodium: a novel dry eye therapy. *Expert Opin Invest Drugs* 2004; 13: 47–54.
2. Tauber J, *et al.* Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea* 2004; 23: 784–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Diquas.

Disodium Guanylate

Disodium Guanosine-5′-monophosphate; E627; Guanilato disódico; Sodium 5′-Guanylate; Гуанилат Натрия Двузамещенный.

Guanosine 5′-(disodium phosphate).

$C_{10}H_{12}N_5Na_2O_8P.xH_2O$=407.2 (anhydrous)

CAS — 5550-12-9 (anhydrous disodium guanylate).

UNII — B76BT44Q8V.

Profile

Disodium guanylate is used in preparations containing other nucleosides in the treatment of corneal damage. Disodium guanylate has been used as a flavour enhancer in foods. The term sodium 5′-ribonucleotide (disodium 5′-ribonucleotide) has been used to refer to a mixture of disodium guanylate with disodium inosinate (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Mon.*: Vitacic.

Disodium Inosinate

Disodium Inosine-5′-monophosphate; E631; Inosinato disódico; Inosinato sódico; Sodium 5′-Inosinate; Инозинат Натрия Двузамещённый; 5′-Inosinato disódico; 5′-Inosinato sódico.

Inosine 5′-(disodium phosphate).

$C_{10}H_{11}N_4Na_2O_8P.xH_2O$=392.2 (anhydrous)

CAS — 4691-65-0 (anhydrous disodium inosinate).

UNII — T2ZYA7KC05.

Profile

Disodium inosinate has been used as a flavour enhancer in foods. It has also been given orally and been applied topically in the treatment of visual disturbance. The term sodium 5′-ribonucleotide has been used to refer to a mixture of disodium inosinate with disodium guanylate (above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Inokat; Lumiclar; Opacout; *Fr.*: Catacol; Correctol; *Ger.*: Antikataraktikum N†.

Disodium Uridine Monophosphate

Disodium UMP; Уридин Монофосфат Динатрий.

5′-Uridylic acid, disodium salt; disodium 5′ uridylate.

$C_9H_{11}N_2O_9PNa_2$=368.1

CAS — 3387-36-8.

Profile

Uridine monophosphate is an endogenous uracil nucleotide involved in many biological processes. Disodium uridine monophosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; disodium uridine diphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Keltican N†; *Spain*: Nucleo CMP; *Ukr.*: Keltican (Келтикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Disulfiram *(BAN, rINN)*

Dissulfiramo; Disulfiraami; Disulfiramas; Disulfirame; Disulfiramo; Disulfiramum; Disulfiram; Ethyldithiourame; TTD; Дисульфирам.

Tetraethylthiuram disulphide; Bis(diethylthiocarbamoyl) disulfide.

$C_{10}H_{20}N_2S_4$=296.5

CAS — 97-77-8.

ATC — N07BB01; P03AA04.

ATC Vet — QN07BB01; QV03AA01.

UNII — TR3MLJ1UAL.

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

Ph. Eur. 8: (Disulfiram). A white or almost white, crystalline powder. M.p. 70 degrees to 73 degrees. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Disulfiram). A white to off-white, odourless crystalline powder. M.p. 69 degrees to 72 degrees. Very slightly soluble in water; soluble 1 in 30 of alcohol and 1 in 15 of ether; soluble in acetone, in carbon disulfide, and in chloroform. Store in airtight containers. Protect from light.

Stability. Studies[1,2] on the stability of disulfiram preparations.

1. Gupta VD. Stability of aqueous suspensions of disulfiram. *Am J Hosp Pharm* 1981; 38: 363–4.
2. Philips M, *et al.* Stability of an injectable disulfiram formulation sterilized by gamma irradiation. *Am J Hosp Pharm* 1985; 42: 343–5.

Uses and Administration

Disulfiram is used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p. 1734.1). Disulfiram is not a cure and the treatment is likely to be of little value unless it is undertaken with the willing cooperation of the patient and is used with supportive psychotherapy.

Disulfiram inhibits aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde, a metabolite of alcohol. The resulting accumulation of acetaldehyde in the blood is widely believed to be responsible for many of the unpleasant symptoms of the disulfiram-alcohol reaction which occur when alcohol is taken, even in small quantities, after disulfiram (see Adverse Effects and Treatment, p. 2496.1). Symptoms can arise within 10 minutes of the ingestion of alcohol and last from half an hour in mild cases to several hours in severe cases. It is advisable to carry out the initial treatment in hospital or in a specialised unit where the patient can be kept under close supervision.

Disulfiram is given orally. In the UK, the dose is 800 mg, taken as a single dose, on the first day of treatment, reduced by 200 mg daily to a maintenance dose which is usually 100 to 200 mg daily. In the USA, where doses above 500 mg daily are not recommended, an initial dose of 500 mg daily for 1 to 2 weeks is given, followed by a maintenance dose of 250 mg daily or within the range of 125 to 500 mg daily. Treatment should be reviewed after no longer than 6 months. Maintenance therapy with disulfiram may need to be continued for months or years, until the patient is fully recovered socially and a basis for permanent self-control has been established.

A test dose of alcohol has been given under close supervision when the patient is receiving maintenance doses of disulfiram, in order to demonstrate the nature of the disulfiram-alcohol reaction. However, these challenge tests are not routinely recommended, and should not in any case be used in patients over 50 years of age. Many authorities consider that an explicit description of the reaction is sufficient.

Disulfiram implants have been used in an attempt to overcome problems of patient compliance but have been largely abandoned due to lack of clinical efficacy.

Alcoholism. References.

1. Wright C, Moore RD. Disulfiram treatment of alcoholism. *Am J Med* 1990; 88: 647–55.
2. Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction* 1997; 92: 381–95.
3. O'Shea B. Disulfiram revisited. *Hosp Med* 2000; 61: 849–51.
4. Brewer C, *et al.* Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs* 2000; 14: 329–341.
5. Suh JJ, *et al.* The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; 26: 290–302.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; disulfiram is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (see Cocaine Withdrawal Syndrome, p. 1986.1).

References.

1. Carroll KM, *et al.* Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004; 61: 264–72.

Adverse Effects and Treatment

Drowsiness and fatigue are common during initial treatment with disulfiram. Other adverse effects reported include a garlic-like or metallic aftertaste, gastrointestinal upsets, body odour, bad breath, headache, impotence, and allergic dermatitis. Peripheral and optic neuropathies, psychotic reactions, and hepatotoxicity may occur.

Disulfiram-alcohol reaction. The use of disulfiram in the management of alcoholism is based on the extremely unpleasant, but generally self-limiting, systemic effects that occur when a patient receiving the drug ingests alcohol. These effects begin with flushing of the face and, as vasodilatation spreads, throbbing in the head and neck and a pulsating headache may develop. Respiratory difficulties, nausea, copious vomiting, sweating, thirst, chest pain, tachycardia, palpitations, marked hypotension, giddiness, weakness, blurred vision, and confusion may follow. The intensity and duration of symptoms is very variable and even small quantities of alcohol may result in alarming reactions. In addition to the above effects, severe reactions have included respiratory depression, cardiovascular collapse, cardiac arrhythmias, myocardial infarction, acute heart failure, unconsciousness, convulsions, and sudden death.

Severe reactions require intensive supportive therapy; oxygen and intravenous fluids may be necessary. Potassium concentrations should be monitored. Giving intravenous ascorbic acid, ephedrine sulfate, or antihistamines has been suggested.

Reviews.

1. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety* 1999; 20: 427–35.

Effects on the blood. There were isolated reports of blood dyscrasias associated with disulfiram in the 1960s. US licensed product information recommends that blood counts should be performed during treatment.

Effects on the liver. A review of 18 cases of hepatitis in patients receiving disulfiram.[1] Symptoms have appeared between 10 days and 6 months after starting disulfiram, and clinical improvement has been seen within 2 weeks of stopping the drug, although liver enzyme values may not return to normal for several months. Fatal hepatic coma had been reported in 7 patients. The clinical picture of disulfiram-induced hepatitis is consistent with a hypersensitivity reaction. Another review[2] evaluated 82 cases of liver injury thought to be due to disulfiram and reported to the Swedish Adverse Drug Reactions Advisory Committee between 1966 and 2002. All but one of the cases were of hepatocellular liver damage, and 4 patients died and 4 underwent liver transplantation. Although there was some evidence that hypersensitivity played a role, it might not be the only mechanism of disulfiram-induced liver disease.

1. Mason NA. Disulfiram-induced hepatitis: case report and review of the literature. *DICP Ann Pharmacother* 1989; 23: 872–4.
2. Björnsson E, *et al.* Clinical characteristics and prognostic markers in disulfiram-induced liver injury. *J Hepatol* 2006; 44: 791–7.

Effects on the nervous system. *ENCEPHALOPATHY.* A 2% incidence of reversible toxic encephalopathy has been reported in patients receiving disulfiram.[1] Onset varies from days to months following the start of therapy and early signs include impaired concentration, memory deficits, anxiety, depression, and somnolence. Confusion and disorientation follow, often accompanied by paranoid delusions and sometimes hallucinations. Other symptoms may include ataxia, loss of fine motor coordination, slurred speech, and intention tremor. The encephalopathy usually resolves within 3 days to 2 weeks of stopping disulfiram, although symptoms may persist for 6 weeks. There are conflicting opinions on whether this psychosis is a toxic reaction to disulfiram or a response to abstinence from alcohol, but the authors suspected that most cases represent a toxic encephalopathy. However, psychosis without any suggestion of encephalopathy has been reported.[2]

1. Hotson JR, Langston JW. Disulfiram-induced encephalopathy. *Arch Neurol* 1976; 33: 141–2.
2. Rossiter SK. Psychosis with disulfiram prescribed under probation order. *BMJ* 1992; 305: 763.

PERIPHERAL NEUROPATHY. Reports of peripheral neuropathy associated with disulfiram and reference to previously reported cases.[1,2] Onset of neuropathy varied from days to months after starting disulfiram treatment and could develop with doses of 250 or 500 mg daily. The most common symptom reported was pins and needles, but numbness, pain/burning, and weakness were frequently described; usually both muscle weakness and sensory loss were noted. Optic atrophy has also been described. Although there might be some improvement immediately after disulfiram withdrawal, the neurological deficit only improved slowly and symptoms might persist for as long as 2 years.[1]

1. Watson CP, *et al.* Disulfiram neuropathy. *Can Med Assoc J* 1980; 123: 123–6.
2. Frisoni GB, Di Monda V. Disulfiram neuropathy: a review (1971-1988) and report of a case. *Alcohol Alcohol* 1989; 24: 429–37.

Effects on the respiratory tract. Bronchospasm and hypertension occurred in an asthmatic patient taking disulfiram after an alcohol challenge test.[1]

1. Zapata E, Orwin A. Severe hypertension and bronchospasm during disulfiram-ethanol test reaction. *BMJ* 1992; 305: 870.

Effects on the skin. Orange-coloured palms and soles, provoking an initial diagnosis of jaundice, developed in a 55-year-old man who had been taking disulfiram for about 2 months.[1] It was postulated that the discoloration was due to accumulation of carotenes in the skin as a result of inhibition of vitamin A metabolism by disulfiram. The discoloration disappeared soon after disulfiram was stopped.

1. Santonastaso M, *et al.* Yellow palms with disulfiram. *Lancet* 1997; 350: 266.

Overdosage. A 6-year-old boy had disulfiram intoxication after receiving disulfiram 250 mg four times daily to a total of 13 doses; he recovered later.[1] Of 6 previous reports one child died and 3 had moderate or severe brain damage. The syndrome of disulfiram intoxication in children is distinct from the disulfiram-alcohol interaction or acute disulfiram intoxication in adults. It is characterised by lethargy or somnolence, weakness, hypotonia, and vomiting, beginning about 12 hours after ingestion and progressing to stupor or coma. Dehydration, moderate tachycardia, and marked tachypnoea occur frequently, muscle tone is greatly decreased, and deep-tendon reflexes may be weak or absent.

Severe neurological damage has also been reported[2] in a 5-year-old girl after acute disulfiram intoxication which was initially diagnosed as diabetic ketoacidosis.

1. Benitz WE, Tatro DS. Disulfiram intoxication in a child. *J Pediatr* 1984; 105: 487–9.
2. Mahajan P, *et al.* Basal ganglion infarction in a child with disulfiram poisoning. *Pediatrics* 1997; 99: 605–8.

Precautions

Disulfiram is contra-indicated in the presence of cardiovascular disease or psychosis or severe personality disorders, and should not be given to patients known to be hypersensitive to it or to other thiuram compounds, such as those used in rubber vulcanisation or pesticides. It should be used with caution in the presence of diabetes mellitus, epilepsy, impaired hepatic or renal function, respiratory disorders, cerebral damage, or hypothyroidism. Caution is also advised when giving disulfiram to those who are addicted to other drugs in addition to alcohol. It is probably best avoided in pregnancy.

Disulfiram should not be given until at least 24 hours after the last ingestion of alcohol. Patients beginning therapy should be fully aware of the disulfiram-alcohol reaction and should be warned to avoid alcohol in any form, including alcohol-containing medicines and alcohol-based topical preparations. Reactions to alcohol may occur as long as 2 weeks after the cessation of disulfiram.

The US manufacturers have recommended that regular blood counts and liver function tests should be performed during long-term therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies disulfiram 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 04/11/11)

Pregnancy. A report of 2 infants with severe limb-reduction anomalies whose mothers had taken disulfiram during pregnancy.[1] Only 2 similar cases had previously been reported.

1. Nora AH, *et al.* Limb-reduction anomalies in infants born to disulfiram-treated alcoholic mothers. *Lancet* 1977; ii: 664.

Interactions

Disulfiram inhibits hepatic enzymes and may interfere with the metabolism of other drugs taken at the same time. It enhances the effects of phenytoin and coumarin anticoagulants and their dosage may need to be reduced. It also inhibits the metabolism and excretion of rifampicin. Toxic reactions have occurred when disulfiram was given with isoniazid or metronidazole. Disulfiram may inhibit the metabolism of paraldehyde leading to an accumulation of acetaldehyde and these drugs should not be used together.

In a study[1] to evaluate the effects of disulfiram on cytochrome P450 isoenzymes, the results suggested that disulfiram-mediated inhibition is mainly selective for CYP2E1 after both acute and chronic dosage.

1. Frye RF, Branch RA. Effect of chronic disulfiram administration on the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and N-acetyltransferase in healthy human subjects. *Br J Clin Pharmacol* 2002; 53: 155–62.

Analgesics. The potential of disulfiram to impair drug metabolism was shown[1] when it was found to prolong the plasma half-life of *phenazone*, probably by inhibiting the hepatic microsomal mixed function oxidases. It was also suggested[1] that disulfiram alters catecholamine metabolism since urinary excretion of vanilmandelic acid was significantly reduced and that of homovanillic acid was increased.

1. Vesell ES, *et al.* Impairment of drug metabolism by disulfiram in man. *Clin Pharmacol Ther* 1971; 12: 785–92.

Antidepressants. It has been reported[1] that *amitriptyline* appeared to enhance the disulfiram-alcohol reaction. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *tricyclic antidepressants* or those inhibiting the same enzymes as disulfiram, such as *MAOIs*.[2]

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; i: 313.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; 305: 1255–62.

Antiprotozoals. For reference to toxicity associated with *metronidazole* given to alcoholic patients who were also receiving disulfiram, see Alcohol, under Interactions of Metronidazole, p. 939.2.

Antipsychotics. It has been suggested[1] that phenothiazine antiemetics such as *chlorpromazine* might increase hypotension because of their α-adrenoceptor blocking activity and should therefore be contra-indicated in patients taking disulfiram. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *phenothiazines*.[2]

1. Kwentus J, Major LF. Disulfiram in the treatment of alcoholism: a review. *J Stud Alcohol* 1979; 40: 428–46.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; 305: 1255–62.

Benzodiazepines. *Diazepam* was reported[1] to reduce the intensity of the disulfiram-alcohol reaction.

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; i: 313.

Cannabis. For a suggestion that a combination of disulfiram and *cannabis* may produce a hypomanic state, see p. 2469.1.

Cardiovascular drugs. Clinically serious pharmacodynamic interactions might be anticipated during the disulfiram-alcohol reaction in patients taking other drugs that impair blood pressure regulation, such as *alpha blockers*, *beta blockers*, or *vasodilators*.[1]

1. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; 305: 1255–62.

Macrolides. Fatal toxic epidermal necrolysis and fulminant hepatitis have been reported[1] after starting *clarithromycin* treatment in a patient who was receiving disulfiram.

1. Masiá M, *et al.* Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. *Arch Intern Med* 2002; 162: 474–6.

Pharmacokinetics

Disulfiram is absorbed variably from the gastrointestinal tract and is rapidly reduced to diethyldithiocarbamate (ditiocarb, p. 1550.2), mainly by the glutathione reductase system in the erythrocytes; reduction may also occur in the liver. Diethyldithiocarbamate is metabolised in the liver to its glucuronide and methyl ester and to diethylamine, carbon disulfide, and sulfate ions. Metabolites are excreted mainly in the urine; carbon disulfide is exhaled in the breath.

There was marked intersubject variability in plasma concentrations of disulfiram and its metabolites in a study of 15 male alcoholics given single oral 250-mg doses of disulfiram and repeated dosing with 250 mg daily for 12 days.[1] Variability might result from the marked lipid solubility of disulfiram, differences in plasma protein binding, or enterohepatic cycling. Average times to reach peak plasma concentrations after single or repeated doses

were 8 to 10 hours for disulfiram, diethyldithiocarbamate, diethyldithiocarbamate-methyl ester, and diethylamine, and for carbon disulfide in breath; peak plasma concentrations of carbon disulfide occurred after 5 to 6 hours. Plasma concentrations of disulfiram were negligible within 48 hours of a dose, although concentrations of some metabolites were still raised. In urine, 1.7 and 8.3% of a disulfiram dose was eliminated as diethyldithiocarbamate-glucuronide in the 24 hours after a single and repeated dose respectively, while diethylamine accounted for 1.6 and 5.7%, respectively. In the 24 hours after a single and repeated dose 22.4 and 31.3%, respectively, was eliminated as carbon disulfide in the breath.

1. Faiman MD, *et al.* Elimination kinetics of disulfiram in alcoholics after single and repeated doses. *Clin Pharmacol Ther* 1984; 36: 520–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Abstensyl; Disulfix; ***Austral.***: Antabuse; ***Austria***: Antabus; ***Belg.***: Antabuse; ***Braz.***: Anti-etanol; Sarcoton; ***Chile***: Antabus; Tolerane†; ***Cz.***: Antabus; ***Denm.***: Antabus; ***Fin.***: Antabus; ***Fr.***: Esperal; ***Ger.***: Antabus†; ***Hung.***: Antaethyl; ***India***: Chronol; De-Quit; Deadict; DFM; Diabuse; Esperal†; Medibuse; NT-Addict; ***Irl.***: Antabuse; ***Ital.***: Antabuse; Etiltox; ***Mex.***: Etabus; ***Neth.***: Antabus; Refusal; ***Norw.***: Antabus; ***NZ***: Antabuse; ***Pol.***: Anticol; ***Port.***: Tetradin; ***Rus.***: Antabus (Антабус); Esperal (Эсперал); Teturam (Тетурам); ***S.Afr.***: Antabuse; ***Singapore***: Antabuse†; ***Spain***: Antabus; ***Swed.***: Antabus; ***Switz.***: Antabus; ***Thai.***: Alcobuse†; Anta-al; Antinol†; Chronol; Difiram; ***Turk.***: Antabus; ***UK***: Antabuse; ***Ukr.***: Esperal (Эсперал); Tetlong (Тетлонг); Teturam (Тетурам); ***USA***: Antabuse.

Multi-ingredient Preparations. ***Rus.***: Lidevine (Лидевин); ***Swed.***: Tenutex; ***Ukr.***: Lidevin (Лидевин).

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

Dizocilpine Maleate *(USAN, rINNM)*

Dizocilpina, maleato de; Dizocilpine, Maléate de; Dizocilpini Maleas; Maleato de dizocilpina; MK-801;. Дизоцилпина Малеат.
(+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a,d*]-cyclohepten-5,10-imine maleate.
$C_{16}H_{15}N.C_4H_4O_4$=337.4
CAS — 77086-21-6 (dizocilpine); 77086-22-7 (dizocilpine maleate).
UNII — 6LR8C1B66Q.

Profile

Dizocilpine is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It has been investigated for its antiepileptic properties as well as for a potential role in various other neurological disorders including the prevention of damage due to cerebral ischaemia.

Dizocilpine has good anticonvulsant activity but as it causes alarming psychotropic effects it was abandoned as a possible therapy for epilepsy.[1] Interest in its use as a possible therapy for stroke continued.

1. Richens A. New antiepileptic drugs. *Br J Hosp Med* 1990; 44: 241.

Dolomite

Доломит.
UNII — UG9H2002BF.

Profile

Dolomite is a naturally occurring mineral composed of calcium and magnesium carbonate. It has been used as a nutritional supplement but may contain lead and other toxic metals and is not generally recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Frutin†; ***USA***: Dolomite.

Dong Quai

Angelica Sinensis; Chinese Angelica; Dang Gui; Dang Qui; Danggui; Донг Квай.
UNII — 697D19QD8N (Angelica sinensis); B66F4574UG (Angelica sinensis root).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii), which specify the root.

Br. includes separate monographs for Angelica Sinensis Root and Processed Angelica Sinensis Root.

Ph. Eur. 8: (Angelica Sinensis Root; Angelicae Sinensis Radix; Processed Angelica Sinensis Root BP 2014). The smoke-dried, whole or fragmented root, with rootlets removed, of *Angelica sinensis*. Diels collected in late autumn. It contains not less than 0.050% of *trans*-ferulic acid, ($C_{10}H_{10}O_4$ = 194.2), calculated with reference to the dried drug.

BP 2014: (Angelica Sinensis Root). The dried whole root of *Angelica sinensis* (*A. polymorpha* var. *sinensis*). It consists of the top (uppermost part), main body, and small lateral roots (tails) collected in late autumn, removed from rootlets and dried. It contains not less than 0.1% of *Z*-ligustilide ($C_{12}H_{14}O_2$ = 190.2), calculated with reference to the dried material. Protect from moisture.

Profile

Dong quai is the dried root of Chinese angelica, *Angelica sinensis* (*A. polymorpha* var. *sinensis*) (Apiaceae). It is used in traditional Chinese medicine in the treatment of menstrual and menopausal disorders, respiratory disorders, and herpes zoster infections.

Other *Angelica* spp. employed in herbal medicine are described on p. 2443.3.

Homoeopathy

Dong quai has been used in homoeopathic medicines under the following names: Angelica sinensis, radix; Angelica sin.

General references.

1. WHO. Radix Angelicae Sinensis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/5.html (accessed 04/02/10)

Interactions. For a suggestion of a potential interaction between dong quai and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Capsella Complex; Dong Quai Complex†; Extralife Meno-Care†; Femi-Nan; Feminine Herbal Complex; Olf†; PM Meno-Care; ***Canad.***: Natural HRT; Phytoestrin; ***Hong Kong***: Phytoestrin†; ***Philipp.***: BSI Medicated Plaster; Spigrow for Girls; ***Singapore***: NeuroAid; Phytoestrin†; ***Ukr.***: Huato Pills (Болюсы Хуато); Lifemin (Лайфемин).

Drosera

Atrapamoscas; Droséra; Droserae Herba; Herba Rorellae; Hierba de la gota; Rorela; Ros Solis; Rossolis; Sonnentau; Sundew; Росянка Круглолистная (*Drosera rotundifolia*).
*ATC Herb — HR03WX5002 (*Drosera rotundifolia: *herb).*
*UNII — 75O014T1HG (*Drosera rotundifolia*).*

Profile

Drosera consists of the air-dried entire plant *Drosera rotundifolia* (Droseraceae) and other *Drosera* spp. Preparations of drosera have been used for its reputed value in respiratory disorders.

Homoeopathy

Drosera has been used in homoeopathic medicines under the following names: Drosera rotundifolia; Dros rot.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Asa Tones†; ***Austria***: Hustensaft Weleda; Pilka Forte; Pilka; ***Belg.***: Saintbois; ***Chile***: Fitotos; Pectoral Pasteur; Pulmagol; Ramistos; ***Cz.***: Tussilen†; ***Fr.***: Pastilles Monleon†; Tussidoron; ***Ger.***: Drosithym-N†; Weleda Hustenelixier; ***India***: Lung-KR; ***Indon.***: Silex; ***Israel***: Pilka; ***Ital.***: Enatus; ***Mex.***: Citos; Fen-y-Tos; ***Port.***: Broncodiazina†; Stodal; ***S.Afr.***: Cough Elixir†; ***Spain***: Pazbronquial; Pilka; ***Switz.***: Bromocod N†; Demo Elixir pectoral N†; DemoPectol; DemoTussil; Drosinula; Elixir contre la toux†; Escotussin; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Nican†; Pastilles bronchiques S; Pilka; Sirop pectoral contre la toux S; Siropectan; Wala Baume pectoral au plantain; ***Venez.***: Codebromil; Dromil Sauco; Pi-Pedrin.

Homoeopathic Preparations. ***Austral.***: Childrens Cough Relief; ***Austria***: Globuli gegen Husten Nr 1; Gripagil Husten- und Bronchialtropfen; Pertudoron†; ***Canad.***: Arum Triphyllum Plex†; Brocosin; Cough & Cold; Drosera Complex; Drosera Homaccord; Drosera Plex†; Homeo-Form R†; Kids Cough & Cold Phytux; L52 Cough & Cold; Pertudoron 1†; Phytotux H; Stodal; ***Chile***: Drosemiel; Pertussin; ***Cz.***: Drosetux; Lehnigrip†; Stodal; ***Fr.***: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Arum Triphyllum Compose; Baudry; Boripharm No 11†; Drosera Complexe No 64; Drosera Compose; Drosetux; Homeogene 14†; Ipeca Compose; L 52; Pates Pectorales; Pertudoron; Stodal; ***Ger.***: A-Bomin; Asthmavowen-N†; Bomapect N; Bronchi-Do; Bronchiselect; Broncho-Entoxin N; Broncho-Injektopas; Drosera-Weliplex†; Erkaltungs-Entoxin; HanoTussan; Infigripp; Jutussin; Monapax; Neolin-Entoxin; Pertudoron 1; Pulmo Bronchialcomplex; Pulmo-cyl Ho-Len-Complex; Pulmosan; Relivora Komplex; Roth's RKT Tropfen; Tussiflorin Hom; Tussisana; Tussistin S; Viropect; ***Hung.***: Drosetux; Stodal; ***Neth.***: Bronchillite; Drosinula; Homeocare siroop; Jutussin R9; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Nectadyn H; Stodal; Tussistin; ***Rus.***: Briacon (Бриакон); Sambucus-Plus (Самбукус-Плюс); Stodal (Стодаль); ***S.Afr.***: Pertudoron Drops†; ***Switz.***: Drosetux; Regenaplex Nr 38b; Stodal; TussEx; ***UK***: Cough Elixir; ***Ukr.***: Stodal (Стодаль).

Drotaverine *(rINN)*

Drotaverina; Drotavérine; Drotaverinum; Дротаверин.
1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline.
$C_{24}H_{31}NO_4$=397.5
CAS — 14009-24-6 (drotaverine); 985-12-6 (drotaverine hydrochloride).
ATC — A03AD02.
ATC Vet — QA03AD02.
UNII — 98QS4N58TW.

Pharmacopoeias. *Pol.* includes Drotaverine Hydrochloride.

Profile

Drotaverine is used as an antispasmodic in the management of biliary-tract, urinary-tract, and gastrointestinal spasm, in usual oral doses of 120 to 240 mg daily in divided doses. It has also been given by intramuscular or intravenous injection.

References.

1. Bolaji OO, *et al.* Pharmacokinetics and bioavailability of drotaverine in humans. *Eur J Drug Metab Pharmacokinet* 1996; 21: 217–21.
2. Romics L *et al.* The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int* 2003; 92: 92–6.
3. Singh KC, *et al.* Drotaverine hydrochloride for augmentation of labor. *Int J Gynaecol Obstet* 2004; 84: 17–22.
4. Gupta B, *et al.* Drotaverine hydrochloride versus hyoscine-N-butylbromide in augmentation of labor. *Int J Gynaecol Obstet* 2008; 100: 244–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: No-Spa (诺仕帕); ***Cz.***: No-Spa; ***Hung.***: No-Spa; ***India***: Atd; Baralgan-D; Cindot; Cyclofas; Detrim; Dortsil; Dotacid; Dotarin; Dotariv; Dotra; Doverin; Dozee; Drobel; Dromac; Dropain; Drot; Drotaspa; Drotikind; Drotin; Drotis; Drotwell; Droty; Drovera; Drovet; Drovit; Dudot; Duraspas; DVN; Eldrot; Emverin; Enzodrot; Inorine; Kydrot; Mefdi; Merispas; Mudot; ***Malaysia***: No-Spa; Zepid; ***Philipp.***: Deolin†; No-Spa†; ***Pol.***: Galospa; No-Spa; ***Rus.***: Bezpa (Беспа)†; No-Spa (Но-Шпа); Nos-Bra (Нош-Бра); Spacovin (Спакованн); Spasmol (Спазмол); Spasmonet (Спазмонет); Spazoverin (Спазоверин); ***Thai.***: Deolin; No-Spa†; Spablock†; Spacovin; Sparax; Sparta; Toverine; ***Ukr.***: No-Spa (Но-Шпа).

Multi-ingredient Preparations. ***Hung.***: Algoflex-M; Algopyrin Complex; No-Spalgin; Paniverin†; Quarelin; ***India***: Abdowin; Abdrot; Apodrot; Baralgan-DM; Coease-M; Detrim; Divo-M; Dora-M; Dortsil-M; Dotarin-MF; Dotra-M; Dozee-M; Drat-MF; Drobel-MF; Drofem; Drofic; Drolid-M; Drolid; Dropar; Drosym-MF; Drotikind-M; Drotin Plus; Drotin-M; Drotmic; Drotwell-M; Dutora-M; DVN Plus; DVN-Forte; Eldrot-Plus; Emverin-MF; Esnil; Fodro-M; Inorine-M; Maff-D; Majispa; Masai; MD-MF; Mefdi; Mefnic-D; Mefsaid-D; Nobel Spas; Novaspas; Ospas; ***Rus.***: Nicospan (НИКОШПАН); No-Spalgin (Но-Шпалгин); Pentalgin (Пенталгин); Unispaz (Юниспаз); Unispaz N (Юниспаз Н); ***Ukr.***: No-Spalgin (Но-Шпалгин)†; Unispas (Юниспаз).

Dulcamara

Argamiel; Bittersüss; Bittersweet; Douce-Amère; Dulcamarae Caulis; Dulce amargo; Hierba mora; Matagallinas; Uvas del diablo; Vid silvestre; Woody Nightshade; Паслён Сладко-горький (*Solanum dulcamara*).
*ATC Herb — HM01AW5022 (*Solanum dulcamara: *stem).*
*UNII — KPS1B1162N (*Solanum dulcamara *top); K4QR93EG7I (*Solanum dulcamara*).*

Profile

Dulcamara consists of the dried stems and branches of *Solanum dulcamara* (Solanaceae). It was formerly a popular remedy for chronic rheumatism and skin eruptions and was given as an infusion.

All parts of the plant are poisonous due to the presence of solanaceous alkaloids. The berries have caused poisoning in children. Adverse effects are treated as described under Atropine, p. 1312.2.

Homoeopathy

Dulcamara has been used in homoeopathic medicines under the following names: Solanum dulcamara; Dulc.

The flowers of *Solanum dulcamara* are also used in homoeopathic medicines under the following names: Dulcamara, Flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Dulcacefak; *Ger.*: Cefabene; *Swed.*: Efabene.

Multi-ingredient Preparations. *Austria*: Dermatodoron; Hustensaft Weleda; *Ger.*: Dermatodoron; Weleda Hustenelixier; *S.Afr.*: Cough Elixir†; Dermatodoron†; Zeel; Zeel; *Switz.*: Elixir contre la toux†.

Homoeopathic Preparations. *Austria*: Echinacea-Cosmoplex; *Canad.*: Angee1†; Arnica-Heel Comp†; Arthflex; Calnor†; Detox L37; Eczema L87; Formula D Doron†; Homeo-S-Asp; Urarthone†; Viburcol; Zeel Comp; *Cz.*: Angin-Heel S; Viburcol; Zeel Compositum; Zeel Salbe†; *Fr.*: Abbe Chaupitre no 18†; Amanita Complexe No 75; Arthro-Drainol; Dermo-Drainol†; Euphrasia Complexe No 115; Homeogene 41†; Homeogrippe†; Juniperus Complexe No 6; Scabiosa Complexe No 87; Soreal; Thuya Complexe No 37; Urarthone; *Ger.*: Bryorheum N; Cysto-Gastreu S R18; Drosera-Weliplex†; Dularell N; G1-Injektopas; Genu-cyl L Ho-Len-Complex; Hewecyst Blasen-Nieren†; Lumbago-Gastreu S R11; Rheuma-Hevert; Rheuma-Hevert; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Symphytum Rowo†; Zeel comp; *Hung.*: Angin-Heel; Viburcol; Zeel; *Neth.*: Apo-Rheum†; Cystilite; Cysto-Gastreu R18; Dulcarhus-Gastreu R11; Gletar; Homeocare Exercito; Omnilite; Prurilite; Reudol; Spiroflor; Zeel comp N; *Rus.*: Atma (Атма); Zeel T (Цель Т); *S.Afr.*: Viburcol; *Switz.*: Regenaplex Nr 28b; Regenaplex Nr 86a; Viburcol N; *UK*: Dermatodoron; *Ukr.*: Atma (Атма).

Ebselen *(rINN)*

DR-3305; Ebsélène; Ebseleno; Ebselenum; PZ-51; Эбсенен.
2-Phenyl-1,2-benzisoselenazolin-3-one.
$C_{13}H_9NOSe$=274.2
CAS — 60940-34-3.
UNII — 40X2P7DPGH.

Profile

Ebselen has antoxidant activity and inhibits lipid peroxidation. It has been investigated as a neuroprotectant in stroke.

References.
1. Yamaguchi T, *et al.* Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. *Stroke* 1998; 29: 12–17.
2. Saito I, *et al.* Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1998; 42: 269–78.

Echinacea

Black Sampson; Blyškiųjų ežuolių šaknys (pale coneflower root); Brauneria; Coneflower; Echinacea angustifolia, racine d' (narrow-leaved coneflower root); Echinacea pallida, racine d' (pale coneflower root); Echinacea purpurea, parties aériennes fleuries d' (purple coneflower herb); Echinacea purpurea, racine d' (purple coneflower root); Echinaceae angustifoliae radix (narrow-leaved coneflower root); Echinaceae pallidae radix (pale coneflower root); Echinaceae purpureae herba (purple coneflower herb); Echinaceae purpureae radix (purple coneflower root); Equinácea; Kaitapäivänhatunjuuri (narrow-leaved coneflower root); Kořen třapatky bledé (pale coneflower root); Kořen třapatky úzkolisté (narrow-leaved coneflower root); Läkerudbeckiarot (pale coneflower root); Liten läkerudbeckiarot (narrow-leaved coneflower root); Rohtopäivänhatunjuuri (pale coneflower root); Rudbeckia; Siauralapių ežuolių šaknys (narrow-leaved coneflower root); Sonnenhutkraut; Эхинацея.

ATC Herb — HL03AW5004 (Echinacea angustifolia: root); HL03AW5003 (Echinacea angustifolia: herb); HL03AW5010 (Echinacea purpurea: whole plant); HL03AW5008 (Echinacea purpurea: herb); HL03AW5006 (Echinacea pallida: herb); HL03AW5009 (Echinacea purpurea: root); HL03AW5005 (Echinacea angustifolia: whole plant); HL03AW5007 (Echinacea pallida: root).

UNII — 4N9P6CC1DX (echinacea); VB06AV5USB (Echinacea angustifolia); D982V7VT3P (Echinacea angustifolia root); 904CK3270L (Echinacea pallida); MGY2W95GWO (Echinacea pallida root); QI7G114Y98 (Echinacea purpurea); OS64WTR4KU (Echinacea purpurea root); 2EMS3QFX65 (Echinacea purpurea flowering top).

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

Ph. Eur. 8: (Narrow-Leaved Coneflower Root; Echinaceae Angustifoliae Radix). The dried, whole, or cut underground parts of *Echinacea angustifolia*. It contains a minimum 0.5% of echinacoside ($C_{35}H_{46}O_{20}$=786.7), calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 8: (Pale Coneflower Root; Echinaceae Pallidae Radix). The dried, whole, or cut underground parts of *Echinacea pallida*. It contains a minimum 0.2% of echinacoside calculated with reference to the dried drug. Store uncomminuted. Protect from light.

Ph. Eur. 8: (Purple Coneflower Herb; Echinaceae Purpureae Herba). The dried, whole or cut flowering aerial parts of *Echinacea purpurea*. It contains a minimum of 0.1% of the sum of caftaric acid ($C_{13}H_{12}O_9$=312.2) and cichoric acid ($C_{22}H_{18}O_{12}$=474.4). Store uncomminuted.

Ph. Eur. 8: (Purple Coneflower Root; Echinaceae Purpureae Radix). The dried, whole or cut underground parts of *Echinacea purpurea*. It contains a minimum of 0.5% of the sum of caftaric acid ($C_{13}H_{12}O_9$=312.2) and cichoric acid ($C_{22}H_{18}O_{12}$=474.4). Store uncomminuted.

USP 36: (Echinacea Angustifolia). It consists of the dried rhizome and roots of *Echinacea angustifolia* (Asteraceae), harvested in the autumn after 1 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Pallida). It consists of the dried rhizome and roots of *Echinacea pallida* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Purpurea Root). It consists of the dried rhizome and roots of *Echinacea purpurea* (Asteraceae), harvested in the autumn after 3 or more years of growth. It contains not less than 0.5% of total phenols. Protect from light.

USP 36: (Echinacea Purpurea Aerial Parts). The aerial parts of *Echinacea purpurea* (Asteraceae) harvested during the flowering stage. It contains not less than 1.0% of chicoric acid, and not less than 0.01% of dodecatetraenoic acid isobutylamides ($C_{16}H_{25}NO$), calculated on the dried basis. Store in airtight containers. Protect from light.

Uses and Administration

Echinacea, the dried, whole, or cut underground parts of *Echinacea angustifolia* (*Brauneria angustifolia*), *E. pallida* (*B. pallida*), or *E. purpurea*, or the aerial parts of *E. purpurea*, is reported to have immunostimulant properties. It is used in herbal preparations for the prophylaxis of bacterial and viral infections.

Homoeopathy

Echinacea has been used in homoeopathic medicines under the following names: Echinacea purp; Echinacea purpurea; Echinacea purpurea ex planta tota; Echinacea purpurea, Planta tota; Echinacea angustifolia; Echin. an.

General references.
1. WHO. Radix Echinaceae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/15.html (accessed 04/02/10)
2. WHO. Herba Echinaceae Purpurae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/16.html (accessed 04/02/10)

Respiratory disorders. Echinacea is widely used in herbal preparations to treat upper respiratory-tract infections such as the common cold. Studies[1-4] have produced conflicting results, but systematic reviews suggest that most have methodological flaws[3] rendering evidence of efficacy unconvincing.[5,6] A meta-analysis[7] of 14 randomised controlled studies suggested that echinacea does have a benefit in decreasing the incidence and duration of the common cold, although it was acknowledged that larger prospective studies controlling for several variables (e.g. species) are needed before it can be routinely recommended. Comparative evaluation of specific preparations is also difficult because of varying composition. Evaluation of the effect of 3 extracts of *Echinacea angustifolia* root, each produced by a different extraction method and with defined phytochemical profiles, showed no clinically significant effects by any of them on experimental rhinovirus infection or ensuing illness compared with placebo.[8] Alkamides, polysaccharides, and caffeic acid derivatives, which have been proposed as the active components of echinacea preparations, were present in varying amounts in the extracts.

1. Turner RB, *et al.* Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob Agents Chemother* 2000; 44: 1708–9.
2. Barrett BP, *et al.* Treatment of the common cold with unrefined echinacea: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; 137: 939–46.
3. Taylor JA, *et al.* Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. *JAMA* 2003; 290: 2824–30.
4. Barrett B, *et al.* Echinacea for treating the common cold: a randomized trial. *Ann Intern Med* 2010; 153: 769–77.
5. Caruso TJ, Gwaltney JM. Treatment of the common cold with echinacea. *Clin Infect Dis* 2005; 40: 807–10.
6. Linde K, *et al.* Echinacea for preventing and treating the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 31/07/08).
7. Shah SA, *et al.* Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *Lancet Infect Dis* 2007; 7: 473–80.
8. Turner RB, *et al.* An evaluation of Echinacea angustifolia in experimental rhinovirus infections. *N Engl J Med* 2005; 353: 341–8.

Adverse Effects and Precautions

The most common adverse effects reported on short-term use of echinacea were gastrointestinal and skin-related; these were generally transient and reversible.[1] Hypersensitivity reactions including anaphylaxis have been reported.[1-4] The MHRA in the UK advises[5] against the use of oral echinacea in children under 12 years of age, because the benefits are outweighed by the low, but potentially severe, risk of allergic reactions in this age group.

1. Huntley AL, *et al.* The safety of herbal medicinal products derived from Echinacea species. *Drug Safety* 2005; 28: 387–400.
2. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002; 88: 42–51.
3. Health Canada. Natural health products and adverse reactions. *Can Adverse React News* 2004; 14(1): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1_e.pdf (accessed 11/08/05)
4. Adverse Drug Reactions Advisory Committee (ADRAC). Adverse reactions to complementary medicines. *Aust Adverse Drug React Bull* 2005; 24: 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.pdf (accessed 11/08/05)
5. MHRA. Press release: echinacea herbal products should not be used in children under 12 years old. (issued 20 August, 2012). Available at: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con180628.pdf (accessed 07/02/13)

Pharmacokinetics

The pharmacokinetics of alkamides extracted from *Echinacea angustifolia* roots have been studied[1] in human subjects. Fast absorption of some alkamides was shown after oral use; highly lipophilic alkamides could not be detected in plasma.

1. Woelkart K, *et al.* Bioavailability and pharmacokinetics of alkamides from the roots of Echinacea angustifolia in humans. *J Clin Pharmacol* 2005; 45: 683–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Echinacin†; *Austria*: Echinacin; Echinaforce; *Belg.*: Echinacin; *Braz.*: Enax; Imunax; Imunnal†; Imunogreen†; *Canad.*: Echinaforce; Echinamide; Super LSN Plus†; Triple Blend Echinacea†; *Cz.*: Echinacin; Immunal; *Ger.*: aar vir; Echiherb†; Echinacin; Echinaforce†; Echinapur†; Echinatur†; Episcorit; Esberitox mono; Immunobion; Lymphozil; Pascotox Purpurea†; Resistan mono; toxiloges†; *Gr.*: Echinacin†; *Hung.*: Echinacin; *Ital.*: EuMunil; *Mex.*: Regripax; *Norw.*: Revitonil; *Pol.*: Echinapur; Echinerba; Immunal; Lymphozil; Purex†; *Rus.*: Estifan (Эстифан); Immunal (Иммунал); Immunex (Иммунекс); Immunorm (Иммунорм); *Spain*: Echinacin; EchinaMed; Ekian†; Revitonil†; *Swed.*: Echinaforce; Echinagard; Echinatex†; Salva vid munsar; *Switz.*: Echinacin; Echinaforce; EchinaMed; Echinapur; Echiplant†; *Thai.*: Echinacin†; Echinax; *Turk.*: Parodontax; *UK*: Cold-n-Flu-Eze; Duchy Herbals Echinacea Relief; Echinaboost; Echinacea; Echinacin; Echinaflu; Echinaforce; Echinapret; EchinEeze; Ekinaclear; Ekinalife; Phytocold; Skin Clear; *Ukr.*: Echinacin (Эхинацин); Immunal (Иммунал); Immuno Theiss (Иммуно Тайсс); Immunoplus (Иммуноплюс); *Venez.*: Flucaps.

Multi-ingredient Preparations. *Arg.*: Novo Prostasan; Parodontax Fluor; SX-22; *Austral.*: Airborne Immunity; Andrographis Complex; Andrographis Compound; Arctium & Zinc Compound; Astragalus Complex; Broncafect; Calporo†; Cats Claw Complex†; Cats Claw-Echine; Cold & Flu Day/Night; DiaCo; Echinacea 4000†; Echinacea ACE + Zinc; Echinacea Citrus Throat; Echinacea Complex†; Echinacea Lozenges; Echinacea Plus Garlix; Echinacea Royale; Esberitox N; Euphrasia Complex; Flavonst; Gartech†; Herbal Throat Spray; Lemsip First Signs Cold & Flu Day + Night; Lemsip First Signs Cold & Flu; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Olive Leaf Plus; Skin Support; Throat-Clear; *Austria*: Esberitox; Parodontax†; Spasmo-Urgenin; Urgenin; *Belg.*: Medica Junior; Urgenin; *Braz.*: Malvatricin Natural Organic†; Malvatricin Natural Soft†; Malvatricin Natural†; Parodontax†; *Canad.*: Cystoforce†; Defense; Echinamide Cold and Cough†; Immune Formula†; *Chile*: Citro-C; Paltomiel Plus; *China*: Esberitox (施保利通); *Cz.*: Lymphozil†; *Fr.*: Alvityl Defenses; Olloseptil Gorge-Larynx; ProstaSecurA; *Ger.*: Esberitox; Euphrasia comp; Schnupfencreme; *Hong Kong*: Perfectil; Urgenin†; Vita Coldycin Echinacea Plus†; *Hung.*: Flu-Vit; Telma; *Indon.*: Actimmune; Bd-GARD; Biofos†; Curmunos; Echinox; Eftian; Ekinase; Elanos Kids; Elanos; Erphacea; Ezygard; Flavin; Formuno; Hepasil; Hepatin; Idesar Plus; Imboost C; Imboost Force; Imboost; Imforce Plus; Imforce; Immu-cea; Immu-cea; Imodul; Imodul; Imox; Imudator; Imufor; Imumax; Imunal Plus; Imunogard; Imunos; Imunos; Imunvit Plus; Imunvit; Kidimun; Neoboost Kids; Neoboost; Norflam; Nufit; Nufit; Ocu-V; Opinacea; Opinacea; Primunox; Proimbus†; Proza; Proza; Stamino; StarMuno; StarMuno; Stimox; Tribost; Vidoran Imun Up; Ximun; *Israel*: Urgenin†; *Ital.*: Body Guard; Cistefi; Coryfin C senza Zucchero; Dermilia Flebozin†; Golatux; Immumil Plus†; Immun-up Junior; Immun-up; Imoviral Junior; Influ-Zinc; Influtux; Lesiorepar; Nepiros; Probigol; Promix 3; Ribovir; Sclerovis H Plus; Ulceclar; *Malaysia*: Esberitox N; *Mex.*: Biomax Kid; *NZ*: Lice Blaster; Strepsils Echinacea Defence†; *Pol.*: Alchinal; Cardiobonisol; Echinasal; Esberitox N; Immunofort; Pectobonisol; Plantifort; Reumaherb; *Port.*: Neo Urgenin; Vitace; *Rus.*: Perfectil (Перфектил); Phyto Novo-Sed (Фито Ново-Сед); Prostanorm (Простанорм); *S.Afr.*: Wecesin†; *Singapore*: Proza; Robovites Multivitamins; *Spain*: Neo Urgenin†; Spasmo-Urgenin; Urgenin†; *Swed.*: Esberitox; Kan Jang; *Switz.*:

A Vogel Spray pour la gorge; Demonatur Capsules contre les refroidissements; Demonatur Dragees pour les reins et la vessie†; Echinadoron; Echinarom; Esberitop; Gel de consoude†; Impuls a la consoude; Kernosan Eau Dentifrice†; Resiston; Resiston; Spagymun; Spagyrom; Wala Echinacea; Wecesin; *Thai.*: Spasmo-Urgenin; *Turk.*: Immuzinc; *UK*: Allerclear; Antifect; Echinacea; Echinaforce Sore Throat Spray; Puerte; Goodypops; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Modern Herbals Cold & Catarrh; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; Revitonil; Sinotar; *Ukr.*: Esberitox (Эсберитокс); Immuno Theiss (Иммуно Тайсс); Immuno-Ton (Іммуно-Тон); Perfectil (Перфектил); Uro-Control (Уро-Контрол); Vitokan (Витохан); *USA*: PowerMate.

Homoeopathic Preparations. *Austral.*: Echine†; Respatona Sore Throat; *Austria*: Echinacea-Cosmoplex; Exangina†; Gripagil-Grippetropfen mit Echinacea; Lymphdiaral; Lymphdiaral; Oculoheel; Otovowen; Sonnenbrandspray; toxi-loges; Traumeel; Zom; *Canad.*: Acne; Angeel†; Arnica-Heel Comp†; Calendula +; Calnor†; Candida Yeast Relief; ClearAc†; Echinacea Compositum; Echinacea L40†; Echinaction†; Euphorbium Compositum; Homeo-Form C†; Hylands Formula CA; Infilex†; Itires; Larydol†; Plant Spray†; Toxex; Traumeel; Yellow Dock Combination†; *Chile*: Calendula Echinacea Comp; Ovukalen; *Cz.*: Dolicoccil†; Galium; Traumeel; *Fr.*: Amanita Complexe No 75; Cistus Canadensis Complexe No 86†; Echinacea Complexe No 40; Hamamelis Compose; Mercurius Cyanatus Complexe No 43†; Symphytum Complexe No 48†; *Ger.*: A-Bomin; Angi Truw N; Cefasept N; Cefasept†; Cefasept; Contramutan; EAP-61; Echinacea comp; Echinacea Urtinktur†; Echinacin akut; Echinaject; Echinarell; Entzundungstropfen; Erkaltungs-Entoxin; Eupatorium N Oligoplex; Flenin; HanoToxin M; Hanotoxin M; Hevertotox; Hevertotox; Immudynal; Immunorell; Infekt 1-Injektopas N; Infekt-Komplex L Ho-Fu-Complex; Infi-Echinacea; Infihepan; Influex; Jowidarmin; Jsoskleran; Lowe-Komplex Nr 5 Echinacea; Lymphdiaral Halstabletten; Lymphdiaral; Lymphozil H; Mato; metabiarex; Mullersche Tabletten; Naranotox; Natuimmun†; Odonton-Echroplex; Original-Tinktur N Truw; Ortitruw; Otovowen; Pascoleucyn N; Pascoleucyn; Pesendorfer; Phonix Thuja-Lachesis spag; phono Gripp; Pulmosan Infekt; Pyrogenium; Regenaplex Haut G; Regenaplex Haut W; Relivora Komplex; Schworotox A; Schworotox; Sinusitis Hevert SL; toxi-loges; toxi-loges; Toxiselect; Traumeel S; Wecesin; Weleda Fieber- und Zahnungszapfchen; Wiedimmun N†; Wiedimmun; *Hung.*: Dolicoccil; Oculoheel; Toxex; Traumeel; *Neth.*: Cold Care; Echilite; Echinacea comp; Febrilite; Homeocare Revito; Infragil; Kruidvat Homeopathie Bzzz†; Lymphdiaral; Mercurius-Heel; Oculoheel; Omnilite; Prrrikweg; Ricura; Rinileen†; Sniffle Care; Toxex; Traumeel S; Vinceel H; *Rus.*: Anabar (Анабар); Cinnabsin (Циннабсин); Mercure-Plus (Меркур-Плюс); Traumeel S (Траумель С); *S.Afr.*: Traumeel S; *Switz.*: Akutur; Contusin; Exsepta; Influaforce†; Multiplex 1; Regenaplex Nr 41a; Traumeel; TussEx; *UK*: Burns Cream; Catarrh Cream; Pyrethrum Spray; WCS Dusting Powder; *Ukr.*: Cinnabsin (Циннабсин); Traumeel S (Траумель С); *USA*: Preferred Remedies Cold & Flu; Traumeel; *Venez.*: Traumeel.

Eculizumab *(BAN, USAN, rINN)*

Eculizumab; Eculizumabum; h5G1.1; Экулизумаб.
Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer.
CAS — 219685-50-4.
ATC — L04AA25.
ATC Vet — QL04AA25.
UNII — A3ULP0F556.

Uses and Administration

Eculizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p. 2485.1) by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia (p. 1122.2). Eculizumab is also used to inhibit thrombotic microangiopathy in patients with atypical haemolytic-uraemic syndrome (p. 1159.1); it is not indicated for haemolytic-uraemic syndrome associated with Shiga toxin producing *Escherichia coli*.

In paroxysmal nocturnal haemoglobinuria, eculizumab is given in a dose of 600 mg once every 7 days for the first 4 weeks, followed by 900 mg 7 days later, and then 900 mg every 12 to 16 days thereafter.

In atypical haemolytic-uraemic syndrome, a dose of 900 mg is given once every 7 days for the first 4 weeks, followed by 1.2 g given 7 days later, and then 1.2 g every 12 to 16 days thereafter. In patients also treated with plasmapheresis or plasma exchange, a supplemental dose of eculizumab 600 mg should be given within 60 minutes after each session. In those given fresh frozen plasma, a supplemental dose of eculizumab 300 mg should be given 60 minutes before each unit of plasma infusion.

Eculizumab is given by intravenous infusion over 25 to 45 minutes. The infusion should be diluted to 5 mg/mL in sodium chloride 0.45% or 0.9%, glucose 5%, or Ringer's injection. The infusion rate may be decreased in the event of infusion reactions but the total infusion time should not exceed 2 hours; the infusion may be stopped in severe reactions. Patients should be monitored for at least one hour after the infusion for signs of infusion reactions. Patients who stop treatment altogether should be monitored for serious reactions (see Adverse Effects, Treatment, and Precautions, below).

Eculizumab should only be given after ensuring adequate vaccination cover, especially meningococcal vaccination (see below).

For the use of eculizumab in children, see below.

Eculizumab is also under investigation in the treatment of neuromyelitis optica.

References.

1. Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. *Lancet* 2009; 373: 759–67.
2. Kelly RJ, *et al.* Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood* 2011; 117: 6786–92.
3. Röth A, Dührsen U. Treatment of paroxysmal nocturnal hemoglobinuria in the era of eculizumab. *Eur J Haematol* 2011; 87: 473–9.
4. McKeage K. Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria. *Drugs* 2011; 71: 2327–45.
5. Loirat C, Prémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011; 6: 60. Available at: http://www.ojrd.com/content/pdf/1750-1172-6-60.pdf (accessed 03/05/12)
6. Lapeyraque A-L, *et al.* Eculizumab in severe Shiga-toxin-associated HUS. *N Engl J Med* 2011; 364: 2561–3.
7. Hodgkins KS, *et al.* Clinical grand rounds: atypical hemolytic uremic syndrome. *Am J Nephrol* 2012; 35: 394–400.
8. Daina E, *et al.* Eculizumab in a patient with dense-deposit disease. *N Engl J Med* 2012; 366: 1161–3. Correction. *ibid.*: 1454.
9. Vivarelli M, *et al.* Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012; 366: 1163–5.
10. Radhakrishnan S, *et al.* Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012; 366: 1165–6.

Administration in children. Eculizumab may be used in children and adolescents in the treatment of atypical haemolytic-uraemic syndrome and of paroxysmal nocturnal haemoglobinuria. For both indications, it is given by intravenous infusion and dosed according to body-weight:

- 5 to < 10 kg: 300 mg weekly in weeks 1 and 2, then once every 3 weeks thereafter
- 10 to < 20 kg: 600 mg in week 1, 300 mg in week 2, then 300 mg every 2 weeks thereafter
- 20 to < 30 kg: 600 mg once weekly for 3 doses, then once every 2 weeks thereafter
- 30 to < 40 kg: 600 mg once weekly for 2 doses, 900 mg at week 3, then 900 mg every 2 weeks thereafter
- 40 kg and over: adult doses (see above)

In patients with atypical haemolytic-uraemic syndrome and also treated with plasmapheresis or plasma exchange, a supplemental dose of eculizumab should be given within 60 minutes after each session. The supplemental dose should be 300 mg when the most recent dose was 300 mg, and should be 600 mg when the most recent dose was 600 mg or more. In patients given fresh frozen plasma, a supplemental dose of eculizumab 300 mg should be given 60 minutes before each unit of plasma infusion.

The concentration and administration of eculizumab infusion is the same as that used in adults (see above), although the infusion time for children less than 12 years of age may be extended to 4 hours if the infusion is slowed because of adverse effects.

Adverse Effects, Treatment, and Precautions

Use of eculizumab increases susceptibility to meningococcal infections and patients should be vaccinated at least 2 weeks before receiving the first dose of eculizumab and receive booster vaccinations according to current guidelines. Prophylactic antibacterial therapy is recommended until 2 weeks after vaccination in patients who are less than 2 years old and those treated with eculizumab less than 2 weeks after vaccination. Patients should be monitored during treatment for early signs of meningococcal infections and treated as required. Patients up to 18 years of age must also be vaccinated against haemophilus influenzae and pneumococcal infections. Susceptibility to other infections may also increase and eculizumab should be used with caution in patients with systemic infection. Other adverse effects that have been reported with eculizumab include hypertension, headache, dizziness, fever, nasopharyngitis, back pain, nausea, vomiting, diarrhoea, leucopenia, thrombocytopenia, and anaemia. Infusion site reactions can include paraesthesia or pain, and hypersensitivity reactions including anaphylaxis have occurred.

Patients who stop eculizumab treatment are at risk for serious reactions. Those with paroxysmal nocturnal haemoglobinuria are at risk of serious haemolysis and should be monitored for at least 8 weeks. Management includes blood transfusion or exchange transfusion, anticoagulation, corticosteroids, or restarting eculizumab. Patients with atypical haemolytic-uraemic syndrome should be monitored for thrombotic microangiopathy for at least 12 weeks after stopping eculizumab. If severe complications occur, restarting eculizumab should be considered, with plasma therapy or appropriate organ-specific supportive care.

Breast feeding. Eculizumab is expected to be distributed into breast milk, but the effect on the breast-fed infant is unknown. See also Pregnancy, below.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies eculizumab 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 06/10/11)

Pregnancy. Eculizumab is expected to cross the placenta, and UK licensed product information suggests that female patients should use effective contraception during and for up to 5 months after stopping therapy. However, the use of eculizumab for the management of paroxysmal nocturnal haemoglobinuria during pregnancy in 8 women has been reported.[1,2] In 3 cases they received the drug in the first trimester, in 3 cases it was continued throughout pregnancy, and in 1 case was given from week 27; in 1 case eculizumab was given in the first 5 weeks of gestation before elective termination. Eculizumab was either undetected or found at very low levels in cord blood at delivery.[1] All babies were healthy at delivery, and found to be developing normally at follow-up, the eldest at 16 months of age.[1,2] It was noted that higher doses of eculizumab were needed to maintain complement blockade in the later stages of pregnancy.[1] Breast milk was analysed in 1 woman during the 10 days after delivery and eculizumab was not detected.[1]

1. Kelly R, *et al.* The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. *Br J Haematol* 2010; 149: 446–50.
2. Marasca R, *et al.* Pregnancy in PNH: another eculizumab baby. *Br J Haematol* 2010; 150: 707–8.

Pharmacokinetics

Eculizumab has an elimination half-life of about 11 to 12 days. Plasma exchange significantly increases eculizumab clearance, and a 1-hour session may reduce concentrations by about 50%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Soliris; *Belg.*: Soliris; *Canad.*: Soliris; *Cz.*: Soliris; *Denm.*: Soliris; *Fr.*: Soliris; *Ger.*: Soliris; *Irl.*: Soliris; *Israel*: Soliris; *Ital.*: Soliris; *Jpn*: Soliris; *Neth.*: Soliris; *Norw.*: Soliris; *Pol.*: Soliris; *Port.*: Soliris; *Spain*: Soliris; *Swed.*: Soliris; *Switz.*: Soliris; *UK*: Soliris; *USA*: Soliris.

Eledoisin *(rINN)*

ELD-950; Eledoisina; Élédoïsine; Eledoisinum; Эледоизин.
5-Oxo-Pro-Pro-Ser-Lys-Asp-Ala-Phe-Ile-Gly-Leu-Met-NH_2;
$C_{54}H_{85}N_{13}O_{15}S$=1188.4
CAS — 69-25-0 (eledoisin); 10129-92-7 (eledoisin trifluoroacetate).
UNII — OKY3285J18.

Profile

Eledoisin is a peptide extracted from the posterior salivary glands of certain small octopuses (*Eledone* spp., Mollusca), or obtained by synthesis. Its actions resemble those of substance P; it is a potent vasodilator and increases capillary permeability. It has been given as the trifluoroacetate in eye drops to stimulate lachrymal secretion in Sjögren's syndrome and other dry eye conditions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Eloisin.

Eniluracil *(BAN, USAN, rINN)*

776C85; Eniluracilo; Eniluracilum; Энилурацил.
5-Ethynyluracil.
$C_6H_4N_2O_2$=136.1
CAS — 59989-18-3.
UNII — 2E2W0W5XIU.

Profile

Eniluracil inactivates the enzyme dihydropyrimidine dehydrogenase, which plays an important role in the metabolism of the antineoplastic fluorouracil (p. 798.1). Eniluracil increases the bioavailability of fluorouracil,

particularly when the latter is given orally. It is being investigated as an adjunct to fluorouracil therapy in the treatment of colorectal, breast, and pancreatic cancer. However, the optimal dose and regimen remains to be determined.

Entsufon Sodium *(USAN, rINNM)*

Entsufón sódico; Entsufon Sodique; Natrii Entsufonum; Натрий Энтсуфон.

Sodium 2-[2-[2-(p-1,3,3-tetramethylbutylphenoxy)ethoxy]ethoxy]ethanesulfonate.

$C_{20}H_{33}NaO_6S$=424.5

CAS — 55837-16-6 (entsufon); 2917-94-4 (entsufon sodium).

UNII — L6867H5FR4.

Profile

Entsufon sodium is a detergent used as a soap substitute for cleansing the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: pHisoHex; *USA*: pHisoHex.

Eprodisate Disodium *(USAN, rINNM)*

Éprodisate Disodique; Eprodisato disódico; Eprodisatum Dinatricum; NC-503; Динатрий Эпродисат.

Disodium propane-1,3-disulfonate.

$C_3H_6Na_2O_6S_2$=248.2

CAS — 36589-58-9.

UNII — 5X0D9H16IU.

NOTE. The names Fibrillex and Kiacta have been used as trade marks for eprodisate disodium.

Profile

Eprodisate disodium is a glycosaminoglycan mimetic under investigation for the prevention of amyloid fibril formation and deposition in the treatment of AA amyloidosis.

References.

1. Dember LM, *et al.* Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med* 2007; 356: 2349–60.
2. Manenti L, *et al.* Eprodisate in amyloid A amyloidosis: a novel therapeutic approach? *Expert Opin Pharmacother* 2008; 9: 2175–80.

Equisetum

Ákerfräken; Asiūklių žolė; Cola de Caballo; Equiseti Herba; Equiseto; Herba Equiseti; Horsetail; Peltokorte; Přeslička; Přeslička nať; Prêle; Prêle, tige de; Schachtelhalmkraut; Ziele skrzypu; Хвощ.

ATC Herb — HD03WX5006 (Equisetum arvense: *herb*); *HG04BW5011* (Equisetum arvense: *herb*); *HG04CW5002* (Equisetum arvense: *herb*).

UNII — 1DP6Y6B65Z (Equisetum arvense *top*); *1L0VKZ185E* (Equisetum arvense *branch*).

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

Ph. Eur. 8: (Equisetum Stem; Horsetail BP 2014). The whole or cut, dried sterile aerial parts of *Equisetum arvense*. It contains a minimum of 0.3% of total flavonoids expressed as isoquercitroside ($C_{21}H_{20}O_{12}$ = 464.4), calculated with reference to the dried drug.

Profile

Equisetum is an ingredient of herbal preparations that have been used in the treatment of genito-urinary and respiratory disorders. Similar preparations have been used in the treatment of cardiovascular disorders, rheumatic disorders, liver disorders, constipation, and as a tonic.

The related species *Equisetum hyemale* (*Equisetum hiemale*) is used in China for the treatment of eye disorders.

Homoeopathy

Equisetum has been used in homoeopathic medicines under the following names: Equisetum arvense; Equisetum arv.

Equisetum hyemale has been used in homoeopathic medicines under the following names: Equisetum hyem.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Silica-Vite†; *Cz.*: Preslicka†; Preslickova†; *Fr.*: Siliprele†; *Ger.*: Nieron E; Redaxa fit†; Salus Zinnkraut; *Ital.*: Bioequiseto†.

Multi-ingredient Preparations. *Arg.*: Adelgazar; Arceligasol; Centella Queen Complex; Centellase Gel; Delgacin; Doctor 10 Body; Natural Diet; Silueta Plus†; *Austral.*: Advanced Bladder Care; Advanced Prostate Care; Advanced Urinary Tract Care; Asa Right Powder†; Cal Alkyline†; Caiporo†; Extralife Fluid-Care†; Hair Skin & Nails; Herniclsc; Nails Hair and Skin; Super One-a-Day Multi; *Austria*: Blasentee St Severin; Entschlackender Abfuhrtee EF-EM-ES; Nierentee St Severin; Pneumopan†; St Bonifatius-Tee†; Uropurat†; *Canad.*: Floradix Kindervital†; Salusan†; *Chile*: Nature Complex Reduct-Te; Perfect Body; Reduc-Te; *Cz.*: Alvisan Neo; Antirevmaticky Caj†; Urcyston Planta; *Fr.*: Alpha Renol; Arterase; Cicatendon; Obeflorine†; Phytemag; Provencale No 2†; Silibiol; Tisane Provencale no 2†; *Ger.*: Equisil N†; Eviprostat N; Hevert-Blasen-Nieren-Tee N†; Imupret; Nephroselect M; Solidagoren; *Hung.*: Urogin; Vensaxa; Vesevedo; *Indon.*: Eviprostat; *Ital.*: Ginecast; Lik-Gel†; Osteo Complex; Osteosil Calcium; Pik Gel; Slimmer Plus; Tripondil; *Jpn*: Eviprostat; *Mex.*: Nordibela; *Philipp.*: Gloww; *Pol.*: Betasol; Cholesol; Doppelherz Energovital Tonik†; Nefrobonisol; NeoFitolizyna†; Reumosol; Sanofil; Urosan†; *Rus.*: Arfazetin-E (Арфазетин-Э); Herbion Urological Drops (Гербион Урологические Капли); Polygemostat (Полигемостат); Tonsilgon N (Тонзилгон Н); *Singapore*: Cystone; Eviprostat; *Spain*: Diurette†; Diurinat; Resolutivo Reglum†; *Switz.*: Nephrosolid; Tisane Diuretique; Urinex; *UK*: Antiglan; Antitis; Aqualente; Kas-Bah; *Ukr.*: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Imupret (Имупрет); Phytolyt (Фитолит); Tonsilgon N (Тонзилгон)†; Urochol (Уроxол)†; Uronephron (Уронефрон); Vitokan (Витокан); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *Venez.*: Demerung; Rheu-Tarx 1.

Homoeopathic Preparations. *Canad.*: Formula Homeo QR 209†; Hylands Formula E; Hylands Kinder-BW; *Fr.*: Millefolium Complexe No 7†; Poconeol no 56; Symphytum Complexe No 48†; Urocalm; *Ger.*: Araniforce rheuma†; Cysto Hevert; Enuroplant N; HanoNephrin; Heweberberol; Infi-Symphytum; Levisticum S; Mandragora comp; Nephroplex; RauwolfiaViscomp; Roth's Rotacard; Steirocall.

Etaden

Ethaden; Этаден.

2-[(6-Amino-1*H*-purin-8-yl)amino]ethanol; 8-[(2-Hydroxyethyl)amino]adenine.

$C_7H_{10}N_6O$=194.2

CAS — 66813-29-4 (etaden); 91297-65-3 (etaden hydrobromide).

Profile

Etaden is used as the hydrobromide monohydrate (dihydrobromide monohydrate) in the form of eye drops to stimulate epithelial regrowth.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Etadexe-Mez (Этадекс-Мез).

Ethanethiol

Ethyl Mercaptan; Thioethyl Alcohol; Ethylmercaptan; Этантиол; Этил Меркаптан.

C_2H_6S=62.13

CAS — 75-08-1.

UNII — M439R54A1D.

Profile

Mercaptans such as ethanethiol have an extremely disagreeable odour that is detectable by humans at very low concentrations and therefore they are added as a safety measure to odourless gases such as natural gas. Inhalation of high concentrations of ethanethiol can cause dizziness, headache, nausea, vomiting, and unconsciousness.

Ethaverine Hydrochloride *(rINNM)*

Etaverina, hidrocloruro de; Éthavérine, Chlorhydrate d'; Etaverini Hydrochloridum; Hidrocloruro de etaverina; Этаверина Гидрохлорид.

6,7-Diethoxy-1-(3,4-diethoxybenzyl)isoquinoline hydrochloride.

$C_{24}H_{29}NO_4.HCl$=432.0

CAS — 486-47-5 (ethaverine); 985-13-7 (ethaverine hydrochloride).

UNII — 6Z6T599E49.

Profile

Ethaverine is the tetraethoxy analogue of papaverine (p. 2362.2) and has been used as the hydrochloride as an antispasmodic in respiratory-tract, biliary, gastrointestinal, and genito-urinary disorders. It has also been used in migraine, vascular disorders and as an antiarrhythmic.

Ethaverine sulfamate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Thai.*: Elzym†.

Ethyl Nitrite

Nitrous Acid Ethyl Ester; Nitrous Ether; Этилнитрит.

$C_2H_5NO_2$=75.07

CAS — 109-95-5.

UNII — 8C7CJ279RV.

NOTE. Do not confuse with *O*-nitrosoethanol, a substance that has been referred to in the literature as 'ethyl nitrite gas'.

Profile

Ethyl nitrite has vasodilator effects similar to other volatile nitrites (see Amyl Nitrite, p. 1540.2). Alcoholic solutions of ethyl nitrite (Ethyl Nitrite Spirit; Nitrous Ether Spirit; Sweet Nitre Spirit; Sp. Aether. Nitros.) have been used as a diaphoretic in the treatment of colds and fevers.

Methaemoglobinaemia occurred in 2 infants given a folk remedy containing ethyl nitrite. Despite treatment with methylthioninium chloride 1 infant died.[1]

1. Chilcote RR, *et al.* Sudden death in an infant from methemoglobinemia after administration of "sweet spirits of nitre". *Pediatrics* 1977; 59: 280–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Witdulsies.

Ethylene Glycol

Alcohol etilénico; Ethylene Alcohol; Etilen Glikol; Etilenglicol; Glicol; Glikol etylenowy; Glycol.

Ethane-1,2-diol.

$C_2H_6O_2$=62.07

CAS — 107-21-1.

UNII — FC72KVT52F.

Uses

Ethylene glycol is commonly encountered in antifreeze solutions and has been used illicitly to sweeten some wines. Diethylene glycol has been used similarly.

Adverse Effects

Toxic effects arising from ingestion of ethylene glycol result from its major metabolites: aldehydes, glycolate, lactate, and oxalate. Clinical features may be divided into three stages depending on the time elapsed since ingestion. In the first 12 hours, the patient may show signs of drunkenness and have nausea and vomiting. Convulsions and neurological defects may occur. From 12 to 24 hours, there may be tachycardia, mild hypertension, pulmonary oedema, and heart failure. Between 24 and 72 hours, patients with severe ethylene glycol poisoning may have flank pain and renal involvement with associated decreased plasma concentrations of calcium and bicarbonate, metabolic acidosis, deposition of oxalate in tissues and kidney tubules, proteinuria, oxaluria, haematuria, and renal failure. There may be respiratory failure, cardiovascular collapse, and sometimes coma and death. The fatal dose is reported to be about 100 mL.

Skin irritation and penetration have been reported after topical application.

Diethylene glycol produces similar toxicity, except that there is no conversion to oxalate and there is greater nephrotoxicity; hepatotoxicity is common. Poisoning has followed adulteration of medicinal products with diethylene glycol.

References.

1. Anonymous. Some wine to break the ice. *Lancet* 1985; ii: 254.
2. Vale JA, Buckley BM. Metabolic acidosis in diethylene glycol poisoning. *Lancet* 1985; ii: 394.
3. Buckley BM, Vale JA. Poisoning by alcohols and ethylene glycol. *Prescribers' J* 1986; 26: 110–15.
4. Lewis LD, *et al.* Delayed sequelae after acute overdoses or poisonings: cranial neuropathy related to ethylene glycol ingestion. *Clin Pharmacol Ther* 1997; 61: 692–9.
5. Hasbani MJ, *et al.* Encephalopathy and peripheral neuropathy following diethylene glycol ingestion. *Neurology* 2005; 64: 1273–5.
6. Schier JG, *et al.* Medication-associated diethylene glycol mass poisoning: a review and discussion on the origin of contamination. *J Public Health Policy* 2009; 30: 127–43.
7. Schep LJ, *et al.* Diethylene glycol poisoning. *Clin Toxicol* 2009; 47: 525–35.

Treatment of Adverse Effects

The stomach may be emptied by gastric aspiration if ingestion of ethylene glycol was within the preceding hour. Severe metabolic acidosis should be corrected. Hypocalcaemia may require correction with calcium gluconate in

severe cases, although this is not usually done routinely because it may increase the formation of calcium oxalate crystals. Haemodialysis may be of value. Alcohol may be given orally or intravenously as it is a competitor of the metabolism of ethylene glycol. Alternatively fomepizole (p. 1553.1), an alcohol-dehydrogenase inhibitor, may be used for the treatment of ethylene glycol poisoning. The value of alcohol or fomepizole in the treatment of diethylene glycol poisoning is unclear.

References.

1. Harry P, *et al.* Ethylene glycol poisoning in a child treated with 4-methylpyrazole. *Pediatrics* 1998; 102: E31.
2. Barceloux DG, *et al.* American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *Clin Toxicol* 1999; 37: 537–60.
3. Brent J, *et al.* Fomepizole for the treatment of ethylene glycol poisoning. *N Engl J Med* 1999; 340: 832–8.
4. Borron SW, *et al.* Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet* 1999; 354: 831.
5. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; 106: 1489–91.
6. Brent J. Current management of ethylene glycol poisoning. *Drugs* 2001; 61: 979–88.
7. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; 36: 1085–9.

Pharmacokinetics

Ethylene glycol is absorbed from the gastrointestinal tract and is metabolised, chiefly in the liver, by alcohol dehydrogenase. Its breakdown products account for its toxicity and include aldehydes, glycolate, lactate, and oxalate.

References.

1. Sivilotti ML, *et al.* Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. *Ann Emerg Med* 2000; 36: 114–25.

Etiproston Trometamol *(rINNM)*

Etiprostón trometamol; Etiproston Tromethamine; Étiprostone Trométamol; Etiprostonum Trometamolum; Этипростон Трометамол.

Trometamol salt of (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*E*)-2-[2-(phenoxymethyl)-1,3-dioxolan-2-yl]vinyl]cyclopentyl]-5-heptenoic acid.

$C_{24}H_{32}O_7,C_4H_{11}NO_3$=553.6

CAS — 59619-81-7 (etiproston).

Profile

Etiproston trometamol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Eucalyptus Leaf

Blahovičníkový list; Eucalypti Folium; Eucalyptus, feuille d'; Eucalyptusblätter; Eukaliptų lapai; Eukaliptuszlevél; Eukalyptuksenlehti; Eukalyptusblad; Лист Эвкалипта.

ATC Herb — HR05WA5010 (Eucalyptus globulus: leaf); HR05WA5009 (Eucalyptus globulus: gum).

UNII — S546YLW6E6 (Eucalyptus globulus leaf).

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

Ph. Eur.: (Eucalyptus Leaf). It consists of the whole or cut dried leaves of older branches of *Eucalyptus globulus*. The whole drug contains not less than 2% v/w of essential oil and the cut drug not less than 1.5% v/w of essential oil, both calculated with reference to the anhydrous drug. It has an aromatic odour of cineole. Protect from light.

Profile

Eucalyptus leaf has been used in oral preparations for coughs and associated respiratory-tract disorders. It is also used as a flavour. It is a source of eucalyptus oil (see below).

General references.

1. WHO. Folium Eucalypti. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/12.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Chlorophyllipt (Хлорофиллипт); Eucalimin (Эвкалимин); Galenofillipt (Галенофиллипт).

Multi-ingredient Preparations. *Arg.*: Farinop; Pre Calent; Repelente Zasu; *Austria*: Euka; *Braz.*: Broncol†; *Canad.*: Formula T13 Tea†; *Chile*: Codetol PM; Paltomiel Plus; Paltomiel; Paltomiel; Pectox; Propolis C; Propolkit; Propolkit; Pulmosina; *Fr.*: Balsofumine; Dolirhume; Olioseptil Gorge-Larynx; Thiopectol; *Ger.*: Cefabronchin; *Hong Kong*: Glycerine Thymol Co†; Uni-Bana†; Vita Coldycin Echinacea Plus†; *India*: Movefast; *Indon.*: Neo Rheumacyl Neck and Shoulder; *Ital.*: Altuss; Fosfoguaiacol†; *Mex.*: Vipooll; *NZ*: Cepacol Sore Throat; Otrivine Menthol; *Rus.*: Elecasol (Элекасол); Evcarom (Эвкаром); Inhaphytol No 2 (Ингафитол 2); Insti (Инсти); Mixture for Inhalations (Смесь Для Ингаляций); *S.Afr.*: Bolus Eucalypti Comp†; *Singapore*: Arkopharma Propolis Spray; *Spain*: Vapores Pyt†; *Switz.*: Eau Precieuse; Silence†; Wala Echinacea; *UK*: Calrub; Collins Elixir Decongesant Pastilles; No-Sor Nose Balm; PainEaze; Revitonil; Sinose; Sudarub; *Ukr.*: Elecasol (Элекасол); Insti (Інсті); *Venez.*: Mixagel.

Homoeopathic Preparations. *Austria*: Bolus Eucalypti Comp; Ferrum Phosphoricum comp; Infludo; Tonsan akut; *Canad.*: Arnica-Heel Comp†; L52 Cough & Cold; *Cz.*: Lehnigrip†; *Fr.*: Cetraria Complexe No 61; Infludo; L 52; *Ger.*: Anovin; Arnica Oligoplex; Gripps; Infigripp; Infludo; Tussistin S; Tussistin; *Neth.*: Grippe-Gastreu R6; Infludo; Kind 0-6 Tussikind; Kruidvat Homeopathie Influ-complex†; Nisyleen; Tussistin; *Rus.*: Phytolacca-Plus (Фитолакка-Плюс); Tonsan-Akut (Тонзан-акут); *Switz.*: Infludo; Regenaplex Nr. 50b; TussEx; *UK*: Bolus Eucalypti Comp; Infludo.

Eucalyptus Oil

Blahovičníková silice; Esencia de eucalipto; Essence d'Eucalyptus Rectifiée; Eucalipto, aceite esencial de; Eucalypti aetheroleum; Eucalypti Etheroleum; Eucalyptus, huile essentielle d'; Eucalyptusöl; Eukaliptų eterinis aliejus; Eukaliptuszolaj; Eukalyptusolja; Eukalyptusöljy; Ökaliptüs Yağı; Olejek eukaliptusowy; Oleum Eucalypti; Эвкалиптовое Масло.

ATC Herb — HR05WA5008 (Eucalyptus globulus: essential oil); HM02AW5004 (Eucalyptus globulus: essential oil).

UNII — 2R04ONI662.

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

Ph. Eur. 8: (Eucalyptus Oil). A colourless or pale yellow liquid with a characteristic aromatic camphoraceous odour. It is obtained by steam distillation and rectification from the fresh leaves or terminal branches of various species of *Eucalyptus* rich in cineole. The species mainly used are *E. globulus*, *E. polybractea*, and *E. smithii*. It contains not less than 70% w/w of cineole. Relative density 0.906 to 0.927. Soluble 1 in 5 of alcohol (70%). Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Eucalyptus oil has been taken orally for catarrh and coughs and is an ingredient of many preparations. It has been used as an inhalation often with other volatile substances. Eucalyptus oil has also been applied as a rubefacient and is used as a flavour. It is also used in aromatherapy.

Adverse Effects and Precautions

The symptoms of poisoning with eucalyptus oil include gastrointestinal symptoms such as epigastric burning, nausea and vomiting, and CNS depression, including coma. Cyanosis, ataxia, miosis, pulmonary damage, delirium, and convulsions may occur. Deaths have been reported.

Oily solutions of eucalyptus oil were formerly used in nasal preparations, but this use is now considered unsuitable as the vehicle inhibits ciliary movements and may cause lipoid pneumonia.

References.

1. Patel S, Wiggins J. Eucalyptus oil poisoning. *Arch Dis Child* 1980; 55: 405.
2. Spoerke DG, *et al.* Eucalyptus oil: 14 cases of exposure. *Vet Hum Toxicol* 1989; 31: 166–8.
3. Webb NJA, Pitt WR. Eucalyptus oil poisoning in childhood: 41 cases in south-east Queensland. *J Paediatr Child Health* 1993; 29: 368–71.
4. Tibballs J. Clinical effects and management of eucalyptus oil ingestion in infants and young children. *Med J Aust* 1995; 163: 177–80.
5. Anpalahan M, Le Couteur DG. Deliberate self-poisoning with eucalyptus oil in an elderly woman. *Aust N Z J Med* 1998; 28: 58.
6. Darben T, *et al.* Topical eucalyptus oil poisoning. *Australas J Dermatol* 1998; 39: 265–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Bosisto's Eucalyptus Spray; *Ger.*: Aspecton Eukaps; Broncho-Truw Erkaltungsbalsam†; Exeu†; Pinimenthol Erkaltungsbad fur Kinder; Pulmotin Inhalat; Rinupret; Schnupfen Kapseln†; Tussidermil N; *Irl.*: MOOV Head Lice†; *Pol.*: Migrenol†; *Port.*: Vicks Vaporub; *Ukr.*: Hedelix Eucaps (Геделикс Эвкалипс).

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

Homoeopathic Preparations. *UK*: Catarrh Cream; Medicinal Gargle; Oleum Rhinale.

Eugenol

Ácido cariofílico; Ácido eugénico; 4-Allylguaiacol; Eugen; Eugenic Acid; Eugénol; Eugenoli; Eugenolis; Eugenolum; Эвгенол.

4-Allyl-2-methoxyphenol.

$C_{10}H_{12}O_2$=164.2

CAS — 97-53-0.

UNII — 3T8H1794QW.

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

Ph. Eur. 8: (Eugenol). A colourless or pale yellow liquid with a strong odour of clove. Practically insoluble in water and in glycerol; freely soluble in alcohol (70%); miscible with alcohol, with glacial acetic acid, with dichloromethane, and with fatty oils. Eugenol darkens in colour on exposure to air. Store in well-filled containers. Protect from light.

USP 36: (Eugenol). It is obtained from clove oil or from other sources. A colourless or pale yellow liquid having a strongly aromatic odour of clove. Upon exposure to air, it darkens and thickens. Slightly soluble in water; miscible with alcohol, with chloroform, with ether, and with fixed oils. Store in airtight containers. Protect from light.

Profile

Eugenol is a constituent of clove oil (p. 2481.3) and some other essential oils. It is used in dentistry, often mixed with zinc oxide, as a temporary anodyne dental filling, and is an ingredient in oral hygiene preparations. Eugenol has been used as a flavour.

Eugenol is an irritant and sensitiser and can produce local anaesthesia. It is reported to inhibit prostaglandin synthesis.

For the pulmonary effects of eugenol inhalation from clove cigarettes, see Abuse, under Clove, p. 2481.3.

References.

1. Sarrami N, *et al.* Adverse reactions associated with the use of eugenol in dentistry. *Br Dent J* 2002; 193: 257–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Analgesico Dental; *Israel*: Mentholatum Toothache Kit; *USA*: Red Cross Toothache.

Multi-ingredient Preparations. *Arg.*: Carnot Topico; *Belg.*: Dentophar†; Olbas; *Chile*: Astrijesan; Listermint Con Fluor†; Parodium; *Cz.*: Alvogyl; *Fr.*: Alodont; Alvogyl; Fluocaril dents sensibles†; Iodopengha†; Pectoderme†; Post-Pengha; Pulparthrol; Pulperyl; Sedapulpe†; Yranol Eugenole; *Gr.*: Counterpain; *Hong Kong*: Counterpain†; Flanil; *Indon.*: Counterpain-PXM; Counterpain; Flexozin; Lafalos Plus; Lafalos; Molakrim; Neo Rheumacyl; Nostren; Nufasic; Painkila; Remakrim†; Stop X; Zeropain; *Irl.*: Ledermix; *Israel*: Alvogyl; Dentin; *Ital.*: Creosoto Composto; Eugenol-Guaiacolo Composto; Gocce Odontalgiche; Odongi; *Malaysia*: Flanil; *Philipp.*: Begesic; Counterpain†; *Rus.*: Parodontocide (Пародонтоцид); *S.Afr.*: Counterpain; *Singapore*: Antipain; Begesic; Counterpain; Flanil; Lafalos Plus; Muscalax; *Spain*: Alvogil†; Piorlis†; *Switz.*: Alvogyl; Benzocaine PD; Ledermix; *Thai.*: Analgen; Analgesic Balm; Begesic; Centropain; Contac Pain; Counterpain Plus; Counterpain; Flanil; Heat Cream; Hot Ize; Masabalm; Methyl Salicylate Cream, Compound; Muscalax; Muscort; Neotica; Nox-Pain; Painza; Patarpain; Reduxpain; Rid-O-Pain; Sancago; SP gel; Stopain; TO Balm; U-Gesic Balm; Voltex; X-Pain; Yapircam; *UK*: Ledermix; *Venez.*: Flemicaine.

Euphorbia

Euforbia; Pill-bearing Spurge; Snake Weed; Молочай.

ATC Herb — HR03WX5003 (Euphorbia hirta: herb).

UNII — 310FI8DJBG (euphorbia); L13YF113GN (Euphorbia pilulifera); 243K8QF0MS (Euphorbia pilulifera extract).

Pharmacopoeias. *Chin.* includes monographs for *Euphorbia humifusa* or *E. maculata* herb and *E. pekinensis* root.

Profile

Euphorbia, the aerial parts of *Euphorbia hirta* (*E. pilulifera*, *Chamaesyce hirta*) (Euphorbiaceae), has sedative and expectorant properties and is used in the treatment of asthma and other respiratory-tract disorders. It has also been used for intestinal amoebiasis.

Other *Euphorbia* spp. are used for a variety of disorders. The seeds and latex of *E. lathyrus* (caper spurge) have been used as a purgative but are too toxic for general use. Many species have been used as arrow poisons.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Tafedim; *India*: Thank God.

Multi-ingredient Preparations. *Austral.*: Asa Tones†; Euphorbia Complex†; ResCo; *Belg.*: Toularynx; *Canad.*: Sirop Cocillana Codeine; *Hong Kong*: Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Compound Cocillana†; Coolding†; *India*: Nefid; *Thai.*: Lactagogue; *UK*: Antibron.

Homoeopathic Preparations. *Austria*: Sensicare; *Canad.*: Lopraxt; *Ger.*: Regenaplex Haut G; *Neth.*: Echilite; *Switz.*: Regenaplex Nr. 71b.

Euphrasia

Augentrost; Eufrasia; Euphraise; Eyebright; Очанка.
ATC Herb — H50TBW5001 (Euphrasia officinalis: *herb*).
UNII — C9842I91WL.

Profile

Euphrasia, the aerial parts of various *Euphrasia* spp. including *E. rostkoviana* and *E. officinalis* (Scrophulariaceae), has been used topically for blepharitis, conjunctivitis, and other eye disorders. However, such use is not generally recommended. Euphrasia has also been used for nasal catarrh and sinusitis, and to prevent snoring.

Homoeopathy

Euphrasia has been used in homoeopathic medicines under the following names: Euphrasia officinalis; Euphrasia ex planta tota; Euph. of.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Allerclear; Snore Calm.

Multi-ingredient Preparations. *Austral.*: Bilberry Plus†; Euphrasia Complex; Euphrasia Compound; Eye Health Herbal Plus Formula 4†; *Ger.*: Euphrasia comp; Herba-Vision Augenbad; Herba-Vision Augentrost; *Indon.*: Oculosan; Proview; *Ital.*: Altacura Ipragocce; Eulux; Iridil; *Singapore*: EyeMax; *Switz.*: Collypan; Herba-Vision Euphrasia; Oculosan; *UK*: Se-Power; Vital Eyes; *Ukr.*: Oko-Health (Око-хелс).

Homoeopathic Preparations. *Austral.*: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Hay Fever; Respatona Head Cold; *Austria*: Apozema Allium Cepa compositum; Apozema Apis compositum; Famulan; Oculoheel; *Canad.*: Allergies; C-Plus; Complete Flu Care 4 Kids†; Endoteel†; Hay Complex†; Hayfever; Homeo-Form S1†; Homeo-S-Asp; Homeodel 15†; Hylamine HF; Hylands Flu; Hylands Formula F; Kids Allergies; Optalia†; Sabalia; Sinus; *Cz.*: Rhinallergy; *Fr.*: Abbe Chaupitre no 66†; Allium Cepa Compose; Dollstamine†; Euphrasia Complexe No 115; Homeoptic; Polyrhinium; Rhinallergy; Uva Ursi Complexe No 9; *Ger.*: ISO-Augentropfen C; Neolin-Entoxin; *Hung.*: Oculoheel; Pro-Aller; *Neth.*: Gletar; Homeoptic†; Oculoheel; *Rus.*: Famulan (Фамулан); Mirticam (Миртикам); *Switz.*: Alceprin-N; Nelsons Pollenna†; Polyrhinium; Regenaplex Nr. 3; Rhinallergy; Spagyrhin; *UK*: Pollenna; *USA*: Preferred Remedies Allergy.

European Barberry

Barberry; Berberry; Jaundice Berry; Oregon Grape; Pepperidge; Pepperidge Bush; Pipperidge; Pipperidge Bush; Sow Berry; Sowberry; Барбарис Обыкновенный (*Berberis vulgaris*).
ATC Herb — HA05AW5003 (Berberis vulgaris: *root bark*); *HA04WX5002* (Berberis vulgaris: *root bark*).
UNII — 492B79913J (Berberis vulgaris); *6XEF22AHC3* (Berberis vulgaris *fruit*); *1TH8Q20J0U* (Berberis vulgaris *root bark*); *ITJ40JX79U* (Berberis vulgaris *root*).

NOTE. The names Barberry, Oregon Grape, and Sowberry have been applied to both European Barberry and Oregon Grape (see p. 2577.1).

Profile

The stem or root bark of the European barberry (*Berberis vulgaris* (Berberidaceae)) is used orally in herbal medicine mainly for hepatic and biliary disorders, as a bitter for dyspepsia, and for some infective diseases. It is used topically in preparations for chronic skin conditions, and in eye washes. The fruit is used for disorders of the gastrointestinal tract and respiratory tract, and as a source of vitamin C.

Berberis vulgaris is a source of berberine (p. 2455.1).

Homoeopathy

European barberry has been used in homoeopathic medicines under the following names: Berberis; Berberis vulgaris; Berber vulg; Berb. vul.; Berberis, fructus; Berberis vulgaris e fructibus; Berberis vulgaris, fructus; Berber vulg, fruct.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Berberis Complex†; Bupleurum Compound; Caprilate†; Gartech†; *Austria*: Amersan; *Canad.*: Biliherb; Bilonat; Depuratif des Trappistes; Herbanat†; Para-Gard; Para-Gone; *Cz.*: Amersan; *Ger.*: Schnupfencreme; *India*: Ampucare; Hepaliv; *Indon.*: Kalkurenal; *Switz.*: Bilifuge; Wala Baume nasal doux; Wala Baume nasal.

Homoeopathic Preparations. *Austria*: Acidum picrinicum Med Complex†; Berberis Cosmoplex†; Erbiode Akne; Erbiode Blasen und Nieren; *Canad.*: Berberis-Homaccord†; Bioactiv R†; Chelidonium Plex†; ClearAc†; Comp-Drops 8 Uri-Tract†; Cynara Complex†; Formula CI 207†; Formula Homeo QR 209†; Hylands Formula CA; Male +; Reneel†; Renelix; Sinall Formula†; *Chile*: Bioactiv R; *Fr.*: Abbe Chaupitre no 6; Berberis Complexe No 83; Boripharm No 1†; Boripharm No 22†; Cholesterolum Complexe No 112†; Cina Compose; Diacure; Digeodren; Hepatodrainol; L 8; Natrum Carbonicum Complexe No 10†; Pareira Brava Compose; Rhus Toxicodendron Compose; Ricinus Compose; Rubia Complexe No 3; Sabal Serrulata Compose; Saponaria Compose; Vascodran; *Ger.*: Alho-Arthrosan N; Anore rheumat; Araniforce arthro; Arthriselect; Arthrokatt; Berberell; Berberis N Oligoplex; Cefarheumin S†; Chola-Plantin N†; Colchicum Complex; Cysto-Gastreu S R18; Doloject; G1-Injektopas; Harnsauretropfen F; Heparanox H; Hevermier Complex N†; Heweberberol; Heweurat N; Hexacyl; Leber-Galletropfen; Lithias-cyl L Ho-Len-Complex; Lumbago-Gastreu S R11; Nierentropfen Cosmochemia; Pesendorfer; Rheucostan R; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; uro-loges; *Neth.*: Acidolite; Cystilite; Cysto-Gastreu R18; Dermalite; Dulcarhus-Gastreu R11; Enulite; Hepalite; Hepatodrainol†; Homeocare Uro; Reneel H; Restructa H; *Port.*: Hepatodrainol; *Rus.*: Berberis Comp (Барбарис Комп); Berberis-Plus (Берберис-Плюс); Helidonium-Plus (Хелидониум-Плюс); Psorilom (Псорилом); *Switz.*: Akutur; metaheptachol; Regenaplex Nr. 21e; Regenaplex Nr. 31b; Regenaplex Nr. 49a; Regenaplex Nr. 51c; *UK*: Catarrh Cream; *Ukr.*: Choledius (Холедиус).

Evening Primrose

King's Cureall; Onagre; Энотера.
ATC Herb — HR03WX5006 (Oenothera biennis: *herb*).
UNII — 76UI55V071 (Oenothera biennis).

Profile

Evening primrose, the aerial parts of *Oenothera biennis* (Onagraceae) and related species of *Oenothera*, is reported to have sedative and astringent properties. It has been used in herbal preparations for respiratory and gastrointestinal disorders.

Evening primrose seed is the source of evening primrose oil (below), which is a source of essential fatty acids.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Sclerovis H Plus.

Evening Primrose Oil

Aceite de prímula; Helokkiöljy; Nakvišų aliejus; Nattljusolja; Oenotherae oleum; Olej wiesiołkowy; Olej wiesiołkowy bezpośredniego tłoczenia (virgin evening primrose oil); Onagra, aceite de; Onagre, huile d'; Pupalkový olej; Macro Энотеры.
ATC Herb — HD11AX5004 (Oenothera biennis: *oil*); *HG02WB5004* (Oenothera biennis: *oil*).
UNII — 3Q9L08K71N.

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

Ph. Eur. 8: (Evening Primrose Oil, Refined; Oenotherae Oleum Raffinatum). The fatty oil obtained from the seeds of *Oenothera biennis* or *O. lamarkiana* by extraction and/or expression, and then refined. A suitable antioxidant may be added. A clear, light yellow or yellow liquid. Relative density about 0.923. Practically insoluble in water and in alcohol; miscible with petroleum spirit (b.p.: 40 degrees to 60 degrees). Store in well-filled, airtight containers under an inert gas. Protect from light.

Uses and Administration

Evening primrose oil is a source of linoleic and gamolenic acid, which are essential fatty acids of the omega-6 series that act as prostaglandin precursors (see p. 2509.2). Evening primrose oil has been given orally for the symptomatic relief of atopic eczema in usual doses of up to 3 grams twice daily; it is also used topically as a cream for the relief of dry or inflamed skin. Evening primrose oil has also been given orally for mastalgia. Evening primrose oil has been studied in a variety of other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome. Mixtures of essential fatty acids (including EF-4, EF-12, and EF-27) derived from evening primrose oil and other oils have also been investigated in various disorders, including diabetic neuropathy, restenosis after angioplasty, and skin damage after radiotherapy.

General references.

1. Kleijnen J. Evening primrose oil. *BMJ* 1994; **309**: 824–5.

Eczema. For the use of evening primrose oil as a source of essential fatty acids for the management of eczema, see under Gamolenic Acid, p. 2509.3.

Mastalgia. For the use of evening primrose oil as a source of gamolenic acid for the management of mastalgia, see p. 2509.3.

Menopausal disorders. Although there are anecdotal reports of benefit, a controlled study[1] found that evening primrose oil was no more effective than placebo for managing menopausal vasomotor symptoms (p. 2245.1).

1. Chenoy R, *et al.* Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994; **308**: 501–3.

Multiple sclerosis. For the use of evening primrose oil in the management of multiple sclerosis, see under Gamolenic Acid, p. 2509.3.

Premenstrual syndrome. For conflicting results from the use of evening primrose oil in premenstrual syndrome see under Gamolenic Acid, p. 2510.1.

Rheumatoid arthritis. For the use of evening primrose oil as a source of gamolenic acid for the management of rheumatoid arthritis, see p. 2510.1.

Adverse Effects and Precautions

See Gamolenic Acid, p. 2510.1.

Effects on the nervous system. Temporal lobe epilepsy was diagnosed after treatment with evening primrose oil in 3 patients who had previously been diagnosed as schizophrenic.[1] Tonic-clonic (grand mal) seizures occurred in 2 additional schizophrenic patients during treatment with evening primrose oil.[2] All of these patients had received or were taking phenothiazine antipsychotics.

1. Vaddadi KS. The use of gamma-linolenic acid and linoleic acid to differentiate between temporal lobe epilepsy and schizophrenia. *Prostaglandins Med* 1981; **6**: 375–9.
2. Holman CP, Bell AFJ. A trial of evening primrose oil in the treatment of chronic schizophrenia. *J Orthomol Psychiatry* 1983; **12**: 302–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Primrose Micelle†; *Fr.*: Osmonagre; *Ger.*: Epogam; Linola gamma; Neobonsen; *Gr.*: Epogam; *Hung.*: Epovit; *India*: Elprim; Simrose; *Irl.*: Naudicelle†; *Malaysia*: Bio-Enhanced Evening Primrose Oil; *NZ*: Efamol; *Philipp.*: Eveprim; *Pol.*: Linoeparol†; Oeparol†; *S.Afr.*: Primolin†; *Swed.*: Efamol; *Switz.*: Epogam; *UK*: Efamol; Evening Gold; Evoprim; Linola Gamma†; *Venez.*: Eve 500.

Multi-ingredient Preparations. *Arg.*: La Edad De Oro; *Austral.*: Arthri Plus†; Arthro-Eze; EPA Compound; For Women Multi Plus EPO†; Ginger-Vite Forte†; Maxepa Evening Primrose Oil; Once Daily Womens Multi; Primrose-E†; Womens One-a-Day Multi; Zellulean with Escin†; *Braz.*: Primoris†; *Canad.*: Primanol Borage Oil†; Restorativ Glucosamine Muscle and Joint; *Fr.*: Anacaps tri-Activ; Anacaps†; Corvitec Derm; Diomega; Dioptec; Donaclim; Donalis; Feminabiane Cycle Feminin; Phaneres; Regederm; Trioptec; *Hong Kong*: Mumomega; Pregnacare; *Hung.*: Allithera; Obesmin; *India*: Bevitplus; Ease-PMS; Edge-P Plus; Edge-P; Goldprim; Multivite Woman; N-Care Forte; *Indon.*: Epocaldi; *Ital.*: Biomineral 5-Alfa; Edemalt; *Malaysia*: Evening Primrose Oil Plus; Prim E; Tocovid Emulsion Plus; *Mex.*: Rodan; *NZ*: Efalex; Efamarine; Efamax†; Mr Nits; *S.Afr.*: CalmolinADD†; Femolin PMS†; *Singapore*: Mumomega Equazen†; Robovites Multivitamins; Seven Seas EPO Plus Starflower Oil; Vita Natal; VitaEPA Plus; *Swed.*: Efalex; Efanatal†; *UK*: Efalex; Efamarine; Efamol PMP; Efanatal; PMT Formula; *Ukr.*: Wellwoman (Вельумен); *USA*: Eucerin Itch-Relief.

Febuprol *(rINN)*

Fébuprol; Febuproll; Febuprolum; Фебупрол.
1-Butoxy-3-phenoxy-2-propanol.
$C_{13}H_{20}O_3$=224.3
CAS — 3102-00-9.
UNII — B5RKR9Y63Y.

Profile

Febuprol is a choleretic that has been given orally in the treatment of biliary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Valbil†.

Felypressin *(BAN, USAN, rINN)* ⊗

Felipresina; Felipresinas; Felipressin; Felypresin; Felypressina; Félypressine; Felypressinum; Phelypressine; PLV2; Фелипрессин.
[2-Phenylalanine,8-lysine]vasopressin; Cys-Phe-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2.
$C_{46}H_{65}N_{13}O_{11}S_2$=1040.2

CAS — 56-59-7.
UNII — 17N2918V6G.

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

Ph. Eur. 8: (Felypressin). A synthetic nonapeptide available as an acetate. A white or almost white powder or flakes. Freely soluble in water; practically insoluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Felypressin is a synthetic analogue of vasopressin (p. 2642.3) with similar actions. Its antidiuretic effects are less than those of vasopressin. It is used as a vasoconstrictor in local anaesthetic injections for dental use when sympathomimetics should be avoided. It is also an ingredient of preparations that have been used in the treatment of pain and inflammation of the mouth.

Preparations

Proprietary Preparations (details are given in Volume B)

Used as an adjunct in:. *Braz.*: Citanest com Octapressin; Citocaína; *Denm.*: Citanest Octapressin; *Fin.*: Citanest Octapressin; *Ger.*: Xylonest; *Hong Kong*: Citanest Octapressin†; *Mex.*: Pristesin F; *Neth.*: Citanest Octapressine; *Norw.*: Citanest Octapressin; *Singapore*: Citanest Octapressin; *Swed.*: Citanest Octapressin; *Turk.*: Citanest Octapressin†; *UK*: Citanest with Octapressin.

Fenchone

Fenchon; Фенхон.
1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one.
$C_{10}H_{16}O$=152.2
CAS — 4695-62-9 ((+)-fenchone); 7787-20-4 ((-)-fenchone); 1195-79-5 ((±)-fenchone).

Profile

Fenchone is a constituent of several essential oils. It has been used in preparations in the treatment of biliary and urinary-tract disorders. It is reported to have counter-irritant properties. Fenchone is also used as a flavour and in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Rowatinex; *Austria*: Rowatinex; *Chile*: Rowatinex; *Cz.*: Rowatinex; *Ger.*: Rowatinex; *Hong Kong*: Neo-Rowatinex; Rowatinex; *Hung.*: Rowatinex; *Irl.*: Rowatinex; *Israel*: Rowatinex; *Malaysia*: Rowatinex; *Philipp.*: Rowatinex; *Pol.*: Rowatinex; *Rus.*: Rowatinex (Роватинекс); *Spain*: Rowanefrin; *Thai.*: Rowatinex; *Venez.*: Rowatinex.

Fencibutirol *(USAN, rINN)*

Fencibutirolum; Mg-4833; Фенцибутирол.
2-(1-Hydroxy-4-phenylcyclohexyl)butyric acid.
$C_{16}H_{22}O_3$=262.3
CAS — 5977-10-6.
UNII — H2V165956A.

Profile

Fencibutirol is a choleretic that has been used in the treatment of constipation and biliary-tract disorders.

Fenipentol *(rINN)*

Fenipentol; Fenipentolum; Фенипентол.
1-Phenylpentan-1-ol; α-Butylbenzyl alcohol.
$C_{11}H_{16}O$=164.2
CAS — 583-03-9.
UNII — X3FZE77O60.

Profile

Fenipentol is a choleretic that has been given orally for the treatment of hepatic and biliary-tract disorders in doses of 100 to 200 mg three times daily. The hemisuccinate and sodium hemisuccinate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Venez.*: Cholipin.

Fennel

Édesköménytermés (bitter fennel); Fänkål, bitter (bitter fennel); Fänkål, söt (sweet fennel); Fenchel; Fenkoli, karvas (bitter fennel); Fenkoli, makea (sweet fennel); Fennel Fruit; Fennel Seed; Fenouil; Fenouil Amer; Fenouil amer, fruit de (bitter fennel); Fenouil doux, fruit de (sweet fennel); Foeniculi amari fructus (bitter fennel); Foeniculi dulcis fructus (sweet fennel); Foeniculum; Fruto de Hinojo; Funcho; Hinojo; Kartieji pankolių vaisiai (bitter fennel); Kerti édesköménytermés (sweet fennel); Owoc kopru włoskiego (bitter fennel); Plod fenyklu obecného pravého (bitter fennel); Plod fenyklu obecného sladkého (sweet fennel); Saldieji pankolių vaisiai (sweet fennel); Фенхель.
ATC Herb — HA03AW5028 (Foeniculum vulgare: fruit); HR05WA5013 (Foeniculum vulgare: fruit).
UNII — 557II4LLC3 (fennel); G3QC02NIE6 (fennel seed).

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

Ph. Eur. 8: (Fennel, Bitter; Foeniculi Amari Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains not less than 4.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 60.0% of anethole and not less than 15.0% of fenchone. Bitter fennel is greenish-brown, brown, or green. Protect from light and moisture.

Ph. Eur. 8: (Fennel, Sweet; Foeniculi Dulcis Fructus). It consists of the dry, cremocarps and mericarps of *Foeniculum vulgare*, subsp. *vulgare*, var. *dulce*. It contains not less than 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. The oil contains not less than 80.0% of anethole. Sweet fennel is pale green or pale yellowish-brown. Protect from light and moisture.

Profile

Fennel is the source of fennel oil (below). It is used as a flavour and carminative, although the efficacy of such traditional remedies in infant colic is considered dubious (see Gastrointestinal Spasm, p. 1807.1). It is also used in herbal remedies for respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Fenyklovy Caj; *Pol.*: Plantex; *Rus.*: Plantex (Плантекс); *Ukr.*: Plantex (Плантекс).

Multi-ingredient Preparations. *Arg.*: Adelgazar; Arceligasol; *Austral.*: Bupleurum Compound; Colon Care; Crampeze Stomach Cramps; Detox Program; Digest Aid; Digestaid; Digestive Aid; *Austria*: Brady's-Magentropfen; Buka; Laxalpin†; Mag Kottas Krauterexpress Abfuhrtee; Planta Lax; *Belg.*: Herbesan; *Braz.*: Balsamo Branco; *Canad.*: Cellutex; Clear Capsules†; Entschlackungstee N†; Floradix Kindervital†; Formula T4†; Gallexier†; Herbal Laxative plus Yogurt†; Herbal Laxative†; *Chile*: Bebe Flat; Draineur; Instalax; Reduc-Te; *Cz.*: Cajova Smes pri Nachlazeni; Detska Cajova Smes; Detsky Caj s Hermankem; Diabetan; Nervova Cajova Smes; Projimava; Pulmoran; Reduktan; Species Pectorales Planta; Stomaran; Zaludecni Cajova Smes; *Fr.*: Afra†; Benetransit†; Bolcitol†; Gastrotisane†; Hepatoflorine†; Mediflor Contre la Constipation Passagere No 7; Mediflor Digestive No 3; Mediflor Diuretique No 4†; Santane D_3†; *Ger.*: Carminativum-Hetterich; Cefabronchin; Floradix Multipretten N; Gallexier; Gastricholan-L; Kneipp Husten- und Bronchial-Tee†; *Hung.*: Babynos; Gallexier; Herbalakt; Mensesyl; Salus Multipretten; Tamarinlax; *India*: Abana; Anti Dysp; Apimore; Aptivate OS; Gasex; Lactacrat; Laxive; Liyurto; Mentat; Naptizer; Paedritone; *Israel*: Jungborn†; *Ital.*: Actenacol; Cadifen; Cadimint; Colimil; Dicalmir; Evamilk; Plurilac; Promolax; Relaxcol; Tripondil; *Jpn*: Anchusan; Cabe 2 New; The Guard Seichojo; *Malaysia*: Taisho Kampo; *Neth.*: Herbesan†; *Pol.*: Amarosal; Bobofen†; DexaPini; Diges-Tonic; Herbapini; Rhelax; Salviasept; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Zlozony†; *Rus.*: Babynos (Бебинос); Insti (Инсти); Phytogastrol (Фитогастрол); Phytonefrol (Фитонефрол); Travisil (Трависил); *Singapore*: Stop Snoring; *Spain*: Crislaxo; *Swed.*: Alpenkraft; Multipretten; *Switz.*: Femisan; Kernosan 24; Kernosan 26; Kernosan Eau Dentifrice†; Kernosan Elixir; Kernosan Heidelberger Poudre; Metabol; Tisane favorisant l'allaitement; Tisane laxative; Tisane pectorale et antitussive; Tisane pour nourissons et enfants; *UK*: Cleansing Herbs; Herbal Indigestion Naturtabs; Indigestion and Flatulence; Lion Cleansing Herbs; Lustys Herbalene; Out-of-Sorts; Pure Plan; Revitonil; Senokot Dual Relief; Sure-Lax (Herbal); *Ukr.*: Apitol (АПИТОЛ); Carminativum Babynos (Карминативум Бебинос); Insti (Інсті); Lipomin (Липомин); Liponorm (Липонорм); Softovak (Софтовак); Travisil (Трависил); Trypsidan (Трипсидан)†.

Homoeopathic Preparations. *Chile*: Cynara Compuesta; *Fr.*: Poconeol no 54.

Fennel Oil

Aetheroleum Foeniculi; Bitterfänkålsolja (bitter-fennel fruit oil); Esencia de Hinojo; Essência de Funcho; Fenouil amer (fruit de), huile essentielle de (bitter-fennel fruit oil); Foeniculi amari fructus aetheroleum (bitter-fennel fruit oil); Hinojo, aceite esencial; Karčiųjų pankolių vaisių eterinis aliejus (bitter-fennel fruit oil); Karvasfenkoliöljy (bitter-fennel fruit oil); Olejek kopru włoskiego (bitter-fennel fruit oil); Oleum Foeniculi; Rezene Yağı; Silice fenyklu hořkého (bitter-fennel fruit oil); Фенхелевое Масло.
ATC Herb — HA03AW5027 (Foeniculum vulgare: essential oil).
UNII — 59AAO5F6HT (fennel oil).

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

Ph. Eur. 8: (Bitter-Fennel Fruit Oil; Foeniculi Amari Fructus Aetheroleum). The essential oil obtained by steam distillation from the ripe fruits of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare*. It contains 12.0 to 25.0% fenchone and 55.0 to 75.0% anethole. A clear, colourless or pale yellow liquid with a characteristic odour. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Bitter-Fennel Herb Oil; Foeniculi Amari Herbae Aetheroleum). The essential oil obtained by steam distillation of the aerial parts of *Foeniculum vulgare*, subsp. *vulgare*, var. *vulgare* collected during fruiting. A clear, pale or intense yellow liquid with an anise-like odour. Store at a temperature not exceeding 25 degrees. The label states that the content is Spanish-type or Tasmanian-type oil.

USNF 31: (Fennel Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Foeniculum vulgare* (Apiaceae). Congealing temperature not lower than 3 degrees. Soluble 1 in 1 of alcohol (90%). If solid matter has separated, carefully warm the oil until it is completely liquefied, and mix before using. Store in airtight containers.

Profile

Fennel oil is used as an aromatic flavour and carminative (but see the comment under Fennel, above); the German expert committee for herbal drugs and preparations (Commission E) considers that the use of fennel oil in infants and toddlers is contra-indicated. It is also used in herbal remedies for respiratory-tract disorders and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Babyfen†; Senefen†; *Pol.*: Plantex; *Rus.*: Plantex (Плантекс); *Ukr.*: Plantex (Плантекс).

Multi-ingredient Preparations. *Austral.*: PulmaCo; ResCo; Throat-Clear; *Austria*: Bucarbon; Luuf-Hustentee; Spasmo Claim†; *Canad.*: Anifen†; *Chile*: Calmatol; *Cz.*: Biotussil; Bronchosan†; Herbadent; Ophthalmo-Septonex; *Fr.*: Dida; *Ger.*: Ephepect-Pastillen N; Floradix Multipretten N; Gastrysat†; Salviathymol N; Verdauungstropfen Gastrofunkten†; Weleda Bronchialbalsam; *Hong Kong*: Magesto; *Hung.*: Cholasyl; Salus Multipretten; Stompax; *India*: Betip; Carmicide DPS; Colicaid; Coliky; Coliwell; Coliza; Cymbi; Decolic Infant; DP-Spas DPS; Gastica; Merispas; Panoric; *Indon.*: Minyak Telon†; *Israel*: Novicarbon†; *Ital.*: Relaxcol; Selezime; *Malaysia*: Eucarbon; *Pol.*: Woodwards Gripe Water; *Rus.*: Bronchosan (Бронхосан); *S.Afr.*: Borsdruppels; Oleum Salviae Comp†; *Swed.*: Alpenkraft; Multipretten; *Switz.*: Eau pour les yeux†; Flatulex; Huile Po-Ho A. Vogel; Laxasan; *Thai.*: Corinap; Gas-Nep; Magesto; *Turk.*: Eucarbon; *Ukr.*: Bronchosan (Бронхосан)†; Eucarbon (Эукарбон); Softovak (Софтовак).

Fenoverine *(rINN)*

Fenoverina; Fénovérine; Fenoverinum; Феноверин.
10-[(4-Piperonyl-1-piperazinyl)acetyl]phenothiazine.
$C_{26}H_{25}N_3O_3S$=459.6
CAS — 37561-27-6.
ATC — A03AX05.
ATC Vet — QA03AX05.
UNII — N274ZQ6PZJ.

Profile

Fenoverine has been used as an antispasmodic but has been withdrawn in some countries after reports of rhabdomyolysis.

Adverse effects. Reports of rhabdomyolysis associated with fenoverine,[1-3] including a fatality.[1] A genetic predisposition has been suggested.[2]

1. Chariot P, *et al.* Fenoverine-induced rhabdomyolysis. *Hum Exp Toxicol* 1995; 14: 654–6.
2. Jouglard J, *et al.* Research into individual predisposition to develop acute rhabdomyolysis attributed to fenoverine. *Hum Exp Toxicol* 1996; 15: 815–20.
3. Chen CW, Chang MH. Rhabdomyolysis induced by fenoverine: a case report and literature review. *Acta Neurol Taiwan* 2005; 14: 143–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Spasmopriv; ***Philipp.***: Spasmopriv; ***Singapore***: Spasmopriv; ***Thai.***: Spasmopriv†.

Fenpipramide *(BAN, rINN)*

Fenpipramid; Fenpipramida; Fenpipramidi; Fenpipramidum; Фенпипрамид.
2,2-Diphenyl-4-piperidinobutyramide.
$C_{21}H_{26}N_2O$=322.5
CAS — 77-01-0.
UNII — 88445508X3.

Fenpipramide Hydrochloride *(BANM, rINNM)*

Fenpipramide, Chlorhydrate de; Fenpipramidi Hydrochloridum; Hidrocloruro de fenpipramida; Фенпипрамида Гидрохлорид.
$C_{21}H_{26}N_2O,HCl$=358.9
CAS — 14007-53-5.
UNII — KJ2V75P034.

Fenpiverinium Bromide *(rINN)*

Bromuro de fenpiverinio; Fenpipramide Methobromide; Fenpipramide Methylbromide; Fenpiverinii Bromidum; Fenpiverinio, bromuro de; Fenpivérinium, Bromure de; Фенпиверинии Бромид.
1-(3-Carbamoyl-3,3-diphenylpropyl)-1-methylpiperidinium bromide; 2,2-Diphenyl-4-piperidinobutyramide methyl bromide.
$C_{22}H_{29}BrN_2O$=417.4
CAS — 125-60-0.
ATC — A03AB21.
ATC Vet — QA03AB21.
UNII — 36479UA8GL.

Profile

Fenpipramide (as the hydrochloride) and its methobromide, fenpiverinium bromide, have been used as antispasmodics. Fenpipramide hydrochloride is also used for its antimuscarinic actions in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Algifen; Analgin; Spasmopan; ***India***: Combispas; Nidi Spas; Nobel Spas; Novaspas; ***Pol.***: Spasmalgon; ***Rus.***: Bioralgin (Биоралгин); Bral (Брал); Bralangine (Бралангин); Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Plenalgin (Пленалгин); Renalgan (Реналган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); ***Thai.***: Donagan; Kanegan†; ***Ukr.***: Baralginus (Баралгинус)†; Novigan (Новиган); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); ***Venez.***: Flemibar.

Fenugreek

Alforva; Alholva; Bockhornsfrö; Bockshornsame; Bockshornsamen; Faenum-Graecum; Fenogreco; Fenugrec; Görögszénamag; Greek hay; Ožragių sėklos; Sarviapilansiemen; Semen Foenugraeci; Semen Trigonellae; Semeno pískavice řeckého sena; Trigonella Foenugraeci Semen; Trigonellae Foenugraeci Semen; Пажитник.
UNII — 5610HF69O8 (fenugreek); 654825W09Z (fenugreek seed); P9K34XXG87 (fenugreek seed resin); 487RI96K8Z (fenugreek leaf).

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

Ph. Eur. 8: (Fenugreek). The dried ripe seeds of *Trigonella foenum-graecum*. It has a strong characteristic odour. Protect from light.

Uses and Administration

Fenugreek has been used as an appetite stimulant and as an ingredient in preparations for respiratory disorders. It also has emollient properties. The tops and seeds are used in cooking.

References.

1. Basch E, *et al.* Therapeutic applications of fenugreek. *Altern Med Rev* 2003; 8: 20–7.
2. Ulbricht C, *et al.* Fenugreek (*Trigonella foenum-graecum* L. Leguminosae): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2007; 7: 143–77.

Adverse Effects

A 5-week-old infant lost consciousness after drinking herbal tea containing fenugreek.[1] On recovery the infant and his urine had an aroma characteristic of that found in 'maple syrup urine disease', an inborn condition involving defective metabolism of branched-chain amino acids. Further investigation revealed that the infant did not have the disease; the aroma was due to the presence of sotolone in the fenugreek seeds used to prepare the tea.

1. Sewell AC, *et al.* False diagnosis of maple syrup urine disease owing to ingestion of herbal tea. *N Engl J Med* 1999; 341: 769.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Fenugrene.

Multi-ingredient Preparations. ***Austral.***: Bilberry Plus†; Garlic and Horseradish + C Complex†; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; ***Fr.***: Phytheol Force†; Trimada; ***India***: Diabasic; Dialife; Happy'tizer†; Lactare; Nobese; ***Indon.***: Lactamam; Milmor NF; Provigor†; ***Malaysia***: Shine Maxtra; ***Philipp.***: Cogent db+; Lungcaire Plus; ***Singapore***: LactaGreek; ***Ukr.***: Alfagin (Алфагин); Pravenor (Правенор); Uronephron (Уронефрон).

Homoeopathic Preparations. *Ger.*: Regenaplex Haut G.

Ferric Chloride

Chlorid železitý hexahydrát; Chlorure Ferrique; Cloruro de hierro III; Ferr. Perchlor.; Ferri Chloridum Hexahydricum; Férrico, cloruro; Ferrikloridhexahydrat; Ferrikloridiheksahydraatti; Ferrique (chlorure) hexahydraté; Ferrum Sesquichloratum; Geležies(III) chloridas heksahidratas; Iron Perchloride; Iron Sesquichloride; Iron Trichloride; Tricloruro de hierro; Vas(III)-klorid-hexahidrát; Żelaza(III) chlorek; Хлорид Железа.
$FeCl_3,6H_2O$=270.3
CAS — 7705-08-0 (anhydrous ferric chloride); 10025-77-1 (ferric chloride hexahydrate).
UNII — U38V3ZVV3V (ferric chloride); 0I2XIN602U (ferric chloride hexahydrate).

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

Ph. Eur. 8: (Ferric Chloride Hexahydrate). A very hygroscopic, crystalline mass or orange-yellow to brownish-yellow crystals. Very soluble in water and in alcohol; freely soluble in glycerol. Store in airtight containers. *Protect from light.*

Profile

Ferric chloride has the general properties of iron salts (p. 2073.1) but is exceptionally astringent. It has been used mainly by local application for its styptic and astringent properties. Local application of ferric chloride or other iron salts may cause permanent discoloration of the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Emostat†; *Ital.*: Cotone Emostatico; ***Rus.***: Hemofer (Гемофер); ***S.Afr.***: Staaldruppels.

Multi-ingredient Preparations. *UK*: Glykola.

Homoeopathic Preparations. *Cz.*: Ferrum Homaccord†; *Ger.*: Infi-China; ***Switz.***: metaossylen N.

Fibronectins

Fibronectina; Фибронектины.

Profile

Fibronectins are high molecular weight endogenous adhesive glycoproteins found in plasma and in the extracellular matrix. Plasma fibronectin was originally known as cold-insoluble globulin. Fibronectins are mainly involved in cellular attachment and migration in normal physiological processes as well as in various malignant diseases. They have an important role in the function of the extracellular matrix, and in morphogenesis and tissue remodelling. They also play a part in aggregation of platelets, and are used in combinations with other blood products in wound-sealant preparations. Manipulation of the activity of fibronectins (for example with fibronectin inhibitors or fibronectin fragments) is being investigated in the treatment of connective tissue diseases, malignancies, and wound healing. Fibronectin itself has potential use as a research tool for the study of cell adhesion and migration processes.

References.

1. Kaspar M, *et al.* Fibronectin as target for tumor therapy. *Int J Cancer* 2006; 118: 1331–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Tisseel Duo†; ***Austria***: Evicel; Tissucol Duo Quick†; Tissucol†; ***Belg.***: Quixil†; Tissucol Duo; Tissucol Kit; ***Canad.***: Tisseel; *Cz.*: Evicel; Tissucol; ***Denm.***: Evicel; Quixil; Tisseel Duo Quick; ***Fin.***: Quixil; Tisseel Duo Quick; ***Fr.***: Evicel; Tissucol; ***Ger.***: Evicel; Quixil†; Tissucol Duo S; Tissucol-Kit; ***Gr.***: Evicel; ***Hong Kong***: Tisseel; ***Hung.***: Tissucol-Kit; ***Irl.***: Evicel; ***Israel***: Tisseel†; ***Ital.***: Quixil; ***Neth.***: Quixil†; Tissucol Duo; Tissucol; ***Norw.***: Evicel; ***NZ***: Tisseel Duo; ***Pol.***: Evicel; ***Rus.***: Tissucol Kit (Тиссукол Кит); ***Spain***: Tissucol Duo; ***Swed.***: Evicel; Quixil†; Tisseel Duo Quick; ***Switz.***: Quixil; Tissucol Duo S†; Tissucol†; ***UK***: Tisseel.

Fingolimod *(rINN)*

Fingolimodum; Финголимод.
2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol.
$C_{19}H_{33}NO_2$=307.5
CAS — 162359-55-9.
ATC — L04AA27.
ATC Vet — QL04AA27.
UNII — 3QN8BYN5QF.

Fingolimod Hydrochloride *(USAN)*

Fingolimod, Chlorhydrate de; Fingolimod Hydrochloride [rINNM (en)] (rINNM); Fingolimodi Hydrochloridum; FTY-720; Hidrocloruro de fingolimod; Финголимода Гидрохлорид.
$C_{19}H_{33}NO_2,HCl$=343.9
CAS — 162359-56-0.
ATC — L04AA27.
ATC Vet — QL04AA27.
UNII — G926EC510T.

Uses and Administration

Fingolimod is an immunomodulator used in the treatment of patients with relapsing forms of multiple sclerosis (p. 996.3), the aim of treatment being to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate, which binds to sphingosine 1-phosphate receptors blocking the emergence of lymphocytes from the lymph nodes thereby reducing the number of lymphocytes into peripheral blood. It is presumed that this reduces the migration of lymphocytes into the CNS.

Fingolimod is given orally as the hydrochloride once daily in a dose equivalent to 500 micrograms of the base. Patients should be observed for 6 hours after the first dose of fingolimod to monitor for signs and symptoms of bradycardia (see Adverse Effects and Precautions, below).

Fingolimod is also under investigation for prophylaxis of acute rejection in kidney transplantation.

References.

1. Kappos L, *et al.* Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* 2006; 355: 1124–40.
2. O'Connor P, *et al.* Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. *Neurology* 2009; 72: 73–9.
3. Leypoldt F, *et al.* Hemorrhaging focal encephalitis under fingolimod (FTY720) treatment: a case report. *Neurology* 2009; 72: 1022–4.
4. Kovarik JM, *et al.* Ketoconazole increases fingolimod blood levels in a drug interaction via CYP4F2 inhibition. *J Clin Pharmacol* 2009; 49: 212–18.
5. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol* 2009; 158: 1173–82.
6. Kappos L, *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 387–401.
7. Cohen JA, *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 402–15.

Adverse Effects and Precautions

The most common adverse effects reported with fingolimod include back pain, cough, diarrhoea, headache, influenza, and elevated liver enzymes.

Reduction in heart rate occurs within one hour of starting fingolimod treatment with maximum reduction in up to 6 hours. Patients should therefore be observed for signs and symptoms of bradycardia for 6 hours after the first dose. Most patients with bradycardia are asymptomatic, but dizziness, fatigue, palpitations, and chest pain may occur in some. After the second dose, a further reduction in heart rate may also occur compared with the heart rate immediately before this second dose, although this change is of smaller magnitude than the reduction on day one. With continued dosing, the heart rate returns to baseline levels within one month of starting treatment. Transient atrioventricular (AV) conduction delays have also occurred at the start of fingolimod treatment, and it is therefore recommended that before treatment starts, a baseline ECG should be obtained for patients at risk of bradyarrhythmia if one has not already been done in the preceding 6 months. These effects on heart rate and AV conduction may recur on

reintroduction of fingolimod if treatment has been stopped for more than 2 weeks, and the precautions for re-initiating treatment outlined above should be followed.

Fingolimod may increase the risk of developing infections due to the reduction in peripheral lymphocyte count (see Uses and Administration, p. 2504.3), and treatment should not be started in patients without a recent full blood count taken within the previous 6 months. Fingolimod should not be started in patients with active acute or chronic infections. Patients should be monitored for signs and symptoms of infection during treatment and for 2 months after treatment has stopped. Stopping fingolimod should be considered if a patient develops a serious infection during treatment, and then the risks versus benefits reassessed before treatment is resumed.

Patients without a history of chickenpox or who have not received varicella-zoster vaccination should be tested for antibodies to varicella-zoster virus. Vaccination should be considered in antibody-negative patients before starting fingolimod treatment, which should then be delayed for one month after vaccination. Giving any live attenuated vaccine should be avoided during, and for 2 months after stopping, fingolimod treatment because of the risk of infection.

Macular oedema has been reported in some patients taking fingolimod, and ophthalmologic evaluation should be carried out before starting treatment and routinely about 3 to 4 months later, and at any time if patients report visual disturbances during treatment. Patients with a history of uveitis and those with diabetes mellitus are at increased risk of developing macular oedema during treatment with fingolimod.

Dyspnoea has been reported with fingolimod and a decrease in lung function tests has been seen in patients as early as 1 month after starting treatment. When considered clinically appropriate, spirometric evaluation of respiratory function and evaluation of diffusion lung capacity for carbon monoxide should be obtained.

Fingolimod may increase liver transaminases and treatment should not be started without results of recent transaminase and bilirubin levels taken within the previous 6 months. Liver enzymes should also be monitored during treatment in patients with signs and symptoms of hepatic impairment, and treatment stopped if significant impairment occurs. The risk of adverse effects with fingolimod may be greater in patients with severe hepatic impairment and consequently they should be monitored closely or treatment avoided.

Hypertension has been reported in patients treated with fingolimod and blood pressure should therefore be monitored during treatment.

Breast feeding. Although there are no human data for excretion of fingolimod in breast milk, it is excreted in the milk of *rats*; therefore, because of the potential for serious adverse reactions in a nursing infant, licensed product information recommends that fingolimod is not compatible with breast feeding.

Pregnancy. Although there are only limited human data for use of fingolimod in pregnancy, developmental toxicity has been shown in *rats* and *rabbits*, and since the sphingosine 1-phosphate receptor is involved in vascular formation during embryogenesis, US licensed product information recommends that fingolimod should only be used during pregnancy if the potential benefit outweighs potential risks to the fetus, which may persist for 2 months after stopping treatment. Additionally, women of child-bearing potential are advised to use effective contraception during fingolimod treatment and for 2 months after treatment stops.

Interactions

Fingolimod should be used with caution at the same time as antineoplastics, immunosuppressants, and immunomodulators because of the increased risk of immunosuppression. Caution should also be exercised when switching patients to fingolimod from long-acting drugs such as *natalizumab* and *mitoxantrone*.

Ketoconazole increases the blood concentrations of fingolimod and fingolimod phosphate, and so patients taking the two drugs together should be closely monitored.

Patients taking *beta blockers*, or class Ia or class III *antiarrhythmics* should be closely monitored when given fingolimod because of the risk of decreased heart rate (see Adverse Effects and Precautions, p. 2504.3).

For use of *vaccines* with fingolimod, see Adverse Effects and Precautions, p. 2504.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gilenya; ***Canad.***: Gilenya; ***Denm.***: Gilenya; ***Fr.***: Gilenya; ***Ger.***: Gilenya; ***Gr.***: Gilenya; ***Irl.***: Gilenya; ***Israel***: Gilenya; ***Jpn***: Gilenya; Imusera; ***Neth.***: Gilenya; ***Norw.***: Gilenya; ***Spain***: Gilenya; ***Swed.***: Gilenya; ***Switz.***: Gilenya; ***Turk.***: Gilenya; ***UK***: Gilenya; ***USA***: Gilenya.

Flavonoid Compounds

Bioflavonoides; Bioflavonoids; Flavonoides; Vitamin P Substances; Vitaminas P; Флавоноиды.

Benzquercin *(rINN)*

Benzquercina; Benzquercine; Benzquercinum; Бензкверцин.
3,3′,4′,5,7-Pentakis(benzyloxy)flavone.
$C_{50}H_{40}O_7$=752.9
CAS — 13157-90-9.
UNII — 499L7I0905.

Diosmin *(BAN, rINN)*

Barosmin; Buchu Resin; Diosmetin 7-Rutinoside; Diosmiini; Diosmina; Diosminas; Diosmine; Diosminum; Diozmin; Диосмин.
3′,5,7-Trihydroxy-4′-methoxyflavone 7-[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranoside].
$C_{28}H_{32}O_{15}$=608.5
CAS — 520-27-4.
ATC — C05CA03.
ATC Vet — QC05CA03.
UNII — 7QM776WJ5N.

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

Ph. Eur. 8: (Diosmin). A greyish-yellow or light yellow hygroscopic powder. Practically insoluble in water and in alcohol; soluble in dimethyl sulfoxide. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

USP 36: (Diosmin). Store in airtight containers.

Ethoxazorutoside *(rINN)*

Aethoxazorutin; Aethoxazorutoside; Ethoxazorutin; Éthoxazorutoside; Ethoxazorutosidum; Etoxazorutósido; Oxarutinum; Этоксазорутозид.
2-Morpholinoethylrutin.
$C_{33}H_{41}NO_{17}$=723.7
CAS — 30851-76-4.

Flavodate Sodium *(rINNM)*

Flavodate de Sodium; Flavodate Disodium; Flavodato sódico; Natrii Flavodas; Натрий Флаводовая.
Disodium (4-oxo-2-phenyl-4*H*-chromene-5,7-diyldioxy) diacetate.
$C_{19}H_{12}Na_2O_8$=414.3
CAS — 37470-13-6 (flavodic acid); 13358-62-8 (flavodate disodium).

Hesperidin

Hesperidiini; Hesperidina; Hesperidinum; Hesperydyna; Гесперидин.
5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-4*H*-chromen-7-yl rutinoside.
$C_{28}H_{34}O_{15}$=610.6
CAS — 520-26-3 (hesperidin); 24292-52-2 (hesperidin methyl chalcone).
UNII — E750O06Y6O.

Description. Hesperidin is a flavonoid isolated from the rind of certain citrus fruits.

Leucocianidol *(rINN)*

Leucocianidolum; Leucocyanidin; Leucocyanidol; Лейкоцианидол.
2-(3,4-Dihydroxyphenyl)chroman-3,4,5,7-tetrol.
$C_{15}H_{14}O_7$=306.3
CAS — 480-17-1.
UNII — RAP1D6110C.

Monoxerutin *(rINN)*

Monohidroxietilrutósidos; Monohydroxyethylrutosides; Monokserutiini; Monoxerutina; Monoxérutine; Monoxerutinum; Моноксерутин.
7-(β-Hydroxyethyl)rutoside.
$C_{29}H_{34}O_{17}$=654.6
CAS — 23869-24-1.
ATC — C05CA02.
ATC Vet — QC05CA02.
UNII — EKF7043SBU.

Oxerutins *(BAN)*

Hidroxiletilrutósidos; Hydroxyethylrutosides; Oxerutinas; Оксерутины.

Description. Oxerutins consist of a mixture of 5 different *O*-(β-hydroxyethyl)rutosides, not less than 45% of which is troxerutin (trihydroxyethylrutoside, below), but which also includes monohydroxyethylrutoside, dihydroxyethylrutoside, and tetrahydroxyethylrutoside.

Quercetin

Quercetina; Кверцетин; 3,3′,4′,5,7-Pentahydroxyflavone.
2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_7$=302.2
CAS — 117-39-5.
UNII — 9IKM0I5T1E (quercetin); 53B03V78A6 (quercetin dihydrate).

Rutoside *(BAN, rINN)*

Rutin; Rutina; Rutosid; Rutosid-Trihydrat; Rutoside trihydraté; Rutosidi; Rutosiditrihydraatti; Rutósido; Rutosidtrihydrat; Rutosidum; Rutosidum Trihydricum; Rutozidas trihidratas; Rutozid-trihidrát; Rutozyd; Rutyna; Рутозид.
2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4-oxo-4*H*-chromen-3-yl rutinoside trihydrate; 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl 6-*O*-(α-L-rhamnosyl)-β-D-glucoside.
$C_{27}H_{30}O_{16}.3H_2O$=664.6
CAS — 153-18-4 (anhydrous rutoside).
ATC — C05CA01.
ATC Vet — QC05CA01.
UNII — 5G06TVY3R7 (anhydrous rutoside); RF4N03853G (rutoside trihydrate).

Description. Rutoside is a flavonoid obtained from buckwheat, *Fagopyrum esculentum* (Polygonaceae), or from other sources which include the flower buds of the Japanese pagoda-tree, *Sophora japonica*, and the leaves of several species of *Eucalyptus*.

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

Ph. Eur. 8: (Rutoside Trihydrate). A yellow or greenish-yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in dichloromethane; soluble in methyl alcohol. It dissolves in solutions of alkali hydroxides. Protect from light.

Troxerutin *(BAN, rINN)*

THR; Trihidroxietilrutina; Trihydroxyethylrutoside; Trioxietilrutina; Trioxyethylrutin; Trokserutiini; Trokserutyna; Troxerutina; Troxérutine; Troxerutinum; Троксерутин.
3′,4′,7-Tris[*O*-(2-hydroxyethyl)]rutin; 5-Hydroxy-7-(2-hydroxyethoxy)-2-{3,4-bis[2-hydroxyethoxy)phenyl]-4-oxo-4*H*-chromen-3-yl rutinoside.
$C_{33}H_{42}O_{19}$=742.7
CAS — 7085-55-4.
ATC — C05CA04.
ATC Vet — QC05CA04.
UNII — 7Y4N11PXO8.

Description. Troxerutin is the principal component of oxerutins, above.

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

Ph. Eur. 8: (Troxerutin). A yellowish-green, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flavonoids are naturally occurring phenolic compounds that are widely distributed in plants, occurring in the free state and also as glycosides. The main types of flavonoids are anthocyanins, chalcones, flavonols, flavones, and flavonones. Flavonoids act as antoxidants and claims have been made for many medicinal uses. Preparations containing natural or semisynthetic flavonoids are thought to improve capillary function by reducing abnormal leakage. They have been given to relieve capillary impairment and venous insufficiency of the lower limbs, and for haemorrhoids.

It has been suggested that flavonoids present in some foods, such as fruit, vegetables, tea, and red wine may protect against the development of atherosclerosis (p. 1250.2).

References.

1. Knekt P. *et al.* Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ* 1996; **312**: 478–81.
2. Hertog MGL. *et al.* Antioxidant flavonols and coronary heart disease risk. *Lancet* 1997; **349**: 699.
3. Youdim KA. *et al.* Dietary flavonoids as potential neuroprotectants. *Biol Chem* 2002; **383**: 503–19.

4. Lopez-Lazaro M. Flavonoids as anticancer agents: structure-activity relationship study. *Curr Med Chem Anticancer Agents* 2002; 2: 691–714.
5. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003; 63: 71–100.
6. Alonso-Coello P, *et al.* Meta-analysis of flavonoids for the treatment of haemorrhoids. *Br J Surg* 2006; 93: 909–20.
7. Cermak R. Effect of dietary flavonoids on pathways involved in drug metabolism. *Expert Opin Drug Metab Toxicol* 2008; 4: 17–35.

Interactions. For a report of quercetin increasing the bioavailability and concentration of ciclosporin, see p. 1954.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dermasistem; Flebon; Flebotropin; Flevomax; Jatamansin NF; Rutilina; Rutosidos; Terbenol; Venoruton; Venosmil; *Austral.*: Paroven; *Austria*: Venoruton; *Belg.*: Docrutosi†; Veinamitol; Ven-Detrex; Venoruton; *Braz.*: Daflon; Flavonid; Venoruton; *Canad.*: Poly C; *Chile*: Flebopex; Insuven; Venoruton; *China*: An Ti Wei Le (安体维乐); Bo Shi Duo Ning (博士多宁); Bu Luo Wei Xin (布络威欣); Bu Rui Jin (布瑞金); Di Wei Xin (迪维欣); Fu Chang (弗畅); FuRui (符瑞); Gai Qu (盖曲); He Tong (禾通); Jiu Ren (久仁); Ka Lun (卡伦); Kai Li Jin Si (凯利金斯); Lang Ning (朗宁); Lin Yuan Luo Ke (林源络克); Lu Ding Nuo (路丁诺); Qi Li (其力); Shi Dan (世丹); Shuai Xing (帅星); Tai Wei Sheng (太韦盛); Wei Qi Ting (卫起汀); WeiXin (纬欣); Xin Chang Fu (欣畅福); Yan Quan (言全); Yi Qu Shan (昌曲善); Yi Xin Jing (益新静); You Ni Ping (尤尼平); Yuan Ting (元汀); ZhiLi (质力); *Cz.*: Cilkanol; Venoruton; *Denm.*: Venoruton; *Fr.*: Dio; Diovenor; Endium†; Flavan; Flebosmil†; Intercyton; Mediveine; Preparation H Veinotonic†; Rheoflux; Sedorrhoide Veinotonique†; Titanoral; Veinamitol; Venaclar; Venirene; *Ger.*: Posorutin†; Rutin-Kapsein; Tovene†; Troxeven; Veno SL; Venoruton†; Venotrulan Trox†; *Gr.*: Liosmin; Radiavit; Rioven; Venoruton; *Hong Kong*: Venosmine; *Hung.*: Dio-PP; Venoruton; *India*: Venusmin; *Indon.*: Ardium; Probien; Venaron; Venosmil; *Israel*: Venoruton; *Ital.*: Alven†; Alvenex; Arvenum; Diosven; Doven; Flebil; Venolen; Venoruton; Venosmine; *Mex.*: Phlebodia; Sies; Teboven; *Neth.*: Venoruton; *NZ*: Paroven; *Philipp.*: Varemoid; Venoruton; *Pol.*: Aflavic; DIH; Diohespan; Diosminex; Otrex; Pelethrocin; Phlebodia; Posorutin; Procto-Hemolan Control; Rutinoven†; Rutoven†; Troxeratio; Venolan; Venoruton; Venotrex; *Port.*: Arvenum†; Arvenum; Hepacalmina; Murallon†; Venex; Veno V; Venoruton; Venosmil; Veroven; *Rus.*: Phlebodia (Флебодиа); Troxevazin (Троксевазин); Venoruton (Венорутон); *S.Afr.*: Paroven†; *Spain*: Esberiven; Venolep; Venorugel; Venoruton; Venosmil; *Switz.*: Hemerven; Pur-Rutin; Venoruton; Venutabs; *Thai.*: Flavon; Heteroid; Venoruton; *Turk.*: Daflon; Natrol Ester C; Vendios; Venoruton; *UK*: Colladeen; Paroven; *Ukr.*: Cyclo 3 Fort (Циклo 3 Форт); Flebodia (Флебодиа); Quertin (Квертин); Troxegel (Троксегель); Vasoket (Вазокет); Venolan (Венолан)†; Venosmil (Веносмил); *USA*: Citro-Flav; Limbrel; *Venez.*: Diovenor; Flavol; Hyflon; Verutil.

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

Homoeopathic Preparations. *Ger.*: Infi-China; Infihepan; Varicylum N.

Flibanserin *(USAN, rINN)*

BIMT-17; BIMT-17BS; Flibanserina; Flibanserine; Flibanserinum; Флибансерин.

1-{2-[4-(α,α,α-Trifluoro-*m*-tolyl)-1-piperazinyl]ethyl}-2-benzimidazolinone.

$C_{20}H_{21}F_3N_4O$=390.4

CAS — 167933-07-5.

ATC — G02CX02.

UNII — 37JK4STR6Z.

Profile

Flibanserin is a 5-HT_{1A}-receptor agonist and 5-HT_{2A}-receptor antagonist that has been investigated in the management of hypoactive sexual desire disorder in premenopausal women.

Flopropione *(rINN)*

Flopropiona; Flopropionum; Fluropropiofenone; Phloropropiophenone; RP-13907; Флопропион.

2′,4′,6′-Trihydroxypropiophenone.

$C_9H_{10}O_4$=182.2

CAS — 2295-58-1.

UNII — 05V5NVB5Y1.

Pharmacopoeias. In *Jpn.*

Profile

Flopropione is an antispasmodic that has been given orally in doses of 40 to 80 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cospanon.

Fluorescein *(BAN)*

Fluoresceina; Fluoresceína; Fluorescéine; Fluoresceinum; Флуоресцеин.

3′,6′-Dihydroxyspiro[isobenzofuran-1(3*H*),9′(9*H*)xanthen]-3-one.

$C_{20}H_{12}O_5$=332.3

CAS — 2321-07-5.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — TPY09G7XIR.

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

Ph. Eur. 8: (Fluorescein). An orange-red, fine powder. Practically insoluble in water; soluble in hot alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Fluorescein). A yellowish-red to red, odourless powder. Insoluble in water; soluble in dilute alkali hydroxides. Store in airtight containers.

Fluorescein Dilaurate *(BANM)*

Fluoresceína, dilaurato de; Флуоресцеина Дилаурат.

$C_{44}H_{56}O_7$=696.9

CAS — 7308-90-9.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — 939U41013O.

Fluorescein Sodium *(BANM)*

CI Acid Yellow 73; Colour Index No. 45350; D & C Yellow No. 8; Fluorescein Natrium; Fluorescein-Natrium; Fluorescein sodná sůl; Fluoresceína sódica; Fluoresceína soluble; Fluorescéine sodique; Fluoresceinnatrium; Fluoresceino natrio druska; Fluoresceinum natricum; Fluoreseiininatrium; Fluoresein Sodyum; Fluoreszcein-nátrium; Obiturin; Resorcinolphthalein Sodium; Sodium Fluorescein; Soluble Fluorescein; Uranin; Uranina; Флуоресцин Натрий.

Disodium fluorescein.

$C_{20}H_{10}Na_2O_5$=376.3

CAS — 518-47-8.

ATC — S01JA01.

ATC Vet — QS01JA01.

UNII — 93X5SPE38X.

NOTE. FLN is a code approved by the BP 2014 for use on single unit doses of eye drops containing fluorescein sodium where the individual container may be too small to bear all the appropriate labelling information. LIDFLN is a similar code approved for eye drops containing lidocaine hydrochloride and fluorescein sodium, and PROXFLN a code for eye drops containing proxymetacaine hydrochloride and fluorescein sodium.

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

Ph. Eur. 8: (Fluorescein Sodium). An orange-red, fine hygroscopic powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane and in hexane. A 2% solution in water has a pH of 7.0 to 9.0. Store in airtight containers. Protect from light.

USP 36: (Fluorescein Sodium). An orange-red, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Uses and Administration

Fluorescein sodium stains damaged cornea and disrupted ocular fluids and is applied to the eye for the detection of corneal lesions and foreign bodies, as an aid to the fitting of hard contact lenses, and in various other diagnostic ophthalmic procedures. It is applied as a 1 or 2% solution as eye drops or as sterile papers impregnated with fluorescein sodium. It may also be given with a local anaesthetic, typically as a 0.25% solution with lidocaine hydrochloride, oxybuprocaine hydrochloride, or proxymetacaine hydrochloride.

Fluorescein sodium may be given by rapid intravenous injection, usually as a solution equivalent to fluorescein 10 or 25%, for retinal angiography. The usual dose is the equivalent of 500 mg of fluorescein. A dose of 7.5 mg/kg has been suggested for children. The oral route has also been tried for angiography. Other uses of intravenous fluorescein sodium have included the differentiation of healthy from diseased or damaged tissue and visualisation of the biliary tract.

Fluorescein dilaurate has been given orally for the assessment of exocrine pancreatic function (see below). Pancreatic enzymes hydrolyse the ester and the amount of free fluorescein excreted in the urine can therefore be taken as a measure of pancreatic activity. A dose of 348.5 mg of fluorescein dilaurate, equivalent to 0.5 mmol of fluorescein, is given with a standard meal, and urine collected for the next 10 hours. The manufacturers give instructions concerning the type and amount of liquid and food which may be taken during this period. A control dose of 188.14 mg of fluorescein sodium, also equivalent to 0.5 mmol of fluorescein, is given on the next day under the same conditions.

Pancreatic function test. Studies of the fluorescein dilaurate test have considered it to be a useful noninvasive screening test for the exclusion of pancreatic exocrine failure in outpatients (see under Pancreatitis, p. 2580.2), particularly those presenting with steatorrhoea[1-3] or chronic diarrhoea.[4] However, low specificity (a relatively high rate of false-positive responses) has been reported with the fluorescein dilaurate test in some patient populations,[2,5] and the need for careful patient instruction in performance of the test has been emphasised.[3] In order to avoid the prolonged collection of urine necessary in the standard test, serum concentrations of fluorescein may be measured several hours after taking the test substance.[6]

The test has been used successfully in children,[7] particularly when the doses of fluorescein dilaurate and fluorescein sodium are reduced and fluid intake modified,[8] although the manufacturers recommend that the commercially available test is not used for this age group. In children, a simplified, single-day test using dual markers, fluorescein dilaurate and mannitol, has been investigated with encouraging results.[9] The fluorescein dilaurate test was found to be more sensitive than the faecal elastase 1 (FE-1) test for the diagnosis of mild-to-moderate exocrine pancreatic insufficiency in a study involving 40 patients.[10] However, a later study[11] involving 45 patients found that the pancreolauryl test was not as accurate at predicting the response to pancreatic enzyme supplements as the FE-1 test.

1. Barry RE, *et al.* Fluorescein dilaurate—tubeless test for pancreatic exocrine failure. *Lancet* 1982; ii: 742–4.
2. Boyd EJS, *et al.* Prospective comparison of the fluorescein-dilaurate test with the secretin-cholecystokinin test for pancreatic exocrine function. *J Clin Pathol* 1982; 35: 1240–3.
3. Gould SR, *et al.* Evaluation of a tubeless pancreatic function test in patients with steatorrhoea in a district general hospital. *J R Soc Med* 1988; 81: 270–3.
4. Murray IA, *et al.* Retrospective audit of the value of the pancreolauryl test in a district general hospital. *Postgrad Med J* 2003; 79: 471–3.
5. Braganza JM. Fluorescein dilaurate test. *Lancet* 1982; ii: 927–8.
6. Dimagno EP. A perspective on the use of tubeless pancreatic function tests in diagnosis. *Gut* 1998; 43: 2–3.
7. Cumming JGR, *et al.* Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test. *Arch Dis Child* 1986; 61: 573–5.
8. Dalzell AM, Heaf DP. Fluorescein dilaurate test of exocrine pancreatic function in cystic fibrosis. *Arch Dis Child* 1990; 65: 788–9.
9. Green MR, *et al.* Dual marker one day pancreolauryl test. *Arch Dis Child* 1993; 68: 649–52.
10. Leodolter A, *et al.* Comparison of two tubeless function tests in the assessment of mild-to-moderate exocrine pancreatic insufficiency. *Eur J Gastroenterol Hepatol* 2000; 12: 1335–8.
11. Elphick DA, Kapur K. Comparing the urinary pancreolauryl ratio and faecal elastase-1 as indicators of pancreatic insufficiency in clinical practice. *Pancreatology* 2005; 5: 196–200.

Pediculosis. Infestation of the eyelashes or eyebrows with pubic lice (p. 2147.3) has been successfully treated with a single application of a 20% solution of fluorescein.[1]

1. Mathew M, *et al.* A new treatment of pthiriasis palpebrarum. *Arch Ophthalmol* 1982; 14: 439–41.

Retinal angiography. Fluorescein is usually given intravenously for retinal angiography, but a study in 20 healthy subjects concluded that an oral dose of fluorescein sodium 25 mg/kg could produce good quality retinal angiograms in the majority of subjects.[1] This study used specially prepared 500-mg capsules of fluorescein sodium; the authors commented that previous oral studies had used the liquid preparation intended for intravenous use. Only mild reactions, possibly due to hypersensitivity, appear to have been reported with oral fluorescein.

1. Watson AP, Rosen ES. Oral fluorescein angiography: reassessment of its relative safety and evaluation of optimum conditions with use of capsules. *Br J Ophthalmol* 1990; 74: 458–61.

Adverse Effects and Precautions

The intravenous injection of fluorescein sodium may produce nausea and vomiting. Extravasation is painful. Hypersensitivity reactions range from urticaria to occasional instances of severe anaphylaxis. Cardiac arrest and fatalities have occurred rarely. Concern that impurities or a defect in manufacturing processes might be responsible for the serious reactions led to a review of the BP specification in the early 1980s and a reduction in the permitted level of impurities. Facilities for resuscitation should be available whenever fluorescein sodium is used intravenously.

Adverse effects after ocular instillation are rare. Allergic-type reactions have been reported and may include allergic conjunctivitis, periorbital oedema, and rashes and urticaria

or angioedema; anaphylaxis has also been reported. Intraocular fluorescein can produce transient blurring of vision, and patients should be warned not to drive or operate machinery until vision is clear.

Transient yellow discoloration of the skin and urine may occur with fluorescein sodium treatment. Contact with fluorescein sodium can stain skin and clothing. Soft contact lenses should not be worn while fluorescein sodium is being used because of the risk of staining.

Oral fluorescein dilaurate should not be given to patients with acute necrotising pancreatitis. Sulfasalazine may interfere with estimations of fluorescein in the fluorescein dilaurate test.

Two large studies have examined the incidence of adverse reactions after intravenous fluorescein angiography. An international survey[1] collected information concerning 594 687 angiographic procedures; the incidence of serious reactions was 1 in 18 020, and that of fatal reactions, 1 in 49 557. Reactions included anaphylactic shock, cardiac arrest, myocardial infarction, and shock with hypotension or respiratory distress. A US survey of 221 781 fluorescein angiograms[2] reported frequency rates of 1 in 63 for a moderate reaction (urticaria, syncope, thrombophlebitis, pyrexia, tissue necrosis, or nerve palsy) and 1 in 1900 for severe reactions (respiratory or cardiac events or tonic-clonic seizures); there was one death.

Individual reports of adverse reactions to intravenous fluorescein sodium include pancreatitis,[3] painful crises in patients with sickle-cell disease,[4] psoriasiform drug eruption,[5] and photoallergy[6] and phototoxicity.[7]

1. Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluoresceinique. *J Fr Ophtalmol* 1983; 6: 495–506.
2. Yannuzzi LA, *et al.* Fluorescein angiography complication survey. *Ophthalmology* 1986; 93: 611–17.
3. Morgan LH, Martin JM. Acute pancreatitis after fluorescein. *BMJ* 1983; 287: 1596.
4. Acheson R, Serjeant G. Painful crises in sickle cell disease after fluorescein angiography. *Lancet* 1985; i: 1222.
5. Mayama M, *et al.* Psoriasiform drug eruption induced by fluorescein sodium used for fluorescein angiography. *Br J Dermatol* 1999; 140: 982–4.
6. Hochsattel R, *et al.* Photoallergic reaction to fluorescein. *Contact Dermatitis* 1990; 22: 42–4.
7. Kearns GL, *et al.* Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985; 107: 796–8.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of fluorescein by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluorescein 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 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fluorescite; Grant; *Austral.*: Disclo-Plaque†; Fluorescite; Fluorets†; Retinofluor; *Canad.*: Ak-Fluor; Bio Glo; Diofluor; Fluorescite; Fluorets; *China*: Fluorescite (历设得); *Cz.*: Fluorescite; *Fin.*: Fluorescite; *Fr.*: Fluocyne; *Gr.*: AK-Fluor; Fluocyne; *Hong Kong*: Fluorescite; Fluorets; *India*: Fluore Stain Strips; Fluresin; *Irl.*: Anatera; Fluorets; *Israel*: Fluorescite; *Ital.*: Fluoralfa; *Malaysia*: Fluorescite; Fluorets; *Mex.*: Optifluor†; *Neth.*: Fluorescite; *Norw.*: Anatera; *NZ*: Fluorescite; Fluorets; *Pol.*: Fluorescite; *Port.*: Fluorescite; *Rus.*: Fluorescite (Флюоресцин); *S.Afr.*: Fluorescite; Fluorets; *Singapore*: Fluorescite; Fluorets; *Swed.*: Fluorescite; *Thai.*: Fluorescite; *Turk.*: Fluorescite; *UK*: Fluorets; *USA*: Ak-Fluor; Bio Glob; Fluor-I-Strip; Fluorescite; Fluorets; Pul-Glo; Funduscein; Ophthifluor.

Multi-ingredient Preparations. *Austral.*: Fluress†; *Austria*: Flurekain†; *Canad.*: Fluoracaine†; Fluress; *Fin.*: Oftan Flurekain; *Ger.*: Thilorbin; *Port.*: Fluotest; *Spain*: Fluotest; *Swed.*: Fluress; *USA*: Fluoracaine; Fluorocaine; Fluorox; Flurate†; Fluress; Flurox; Healon Yellow†.

Pharmacopoeial Preparations

BP 2014: Fluorescein Eye Drops; Fluorescein Injection;
USP 36: Fluorescein Injection; Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution; Fluorescein Sodium and Proparacaine Hydrochloride Ophthalmic Solution; Fluorescein Sodium Ophthalmic Strips.

Formic Acid

Ácido amínico; Ácido formílico; Ácido metánico; Acidum Formicum; Ameisensäure; Aminic Acid; E236; E237 (formiato sódico); E237 (sodium formate); E238 (calcium formate); E238 (formiato cálcico); Fórmico, ácido; Kwas mrówkowy.
CH_2O_2=46.02
CAS — 64-18-6.
ATC Vet — QP53AG01.
UNII — 0YIW783RG1.

Pharmacopoeias. In *Pol.*

Profile

Formic acid resembles acetic acid in its properties (see p. 2427.1) but is more irritating and pungent. The acid and its sodium and calcium salts are used as preservatives in food. Solutions containing about 60% formic acid have been marketed for the removal of lime scale from kettles. Formic acid has also been used for the removal of tattoos. It is an ingredient of some external preparations promoted for the relief of musculoskeletal and joint disorders, and has been used with benzyl alcohol to aid the removal of nits.

In a report of 3 patients who swallowed descaling agents containing 40 or 55% formic acid, the major complications included local corrosive effects, metabolic acidosis, derangement of blood-clotting mechanisms, and acute onset of respiratory and renal failure.[1] All 3 patients died between 5 and 14 days after admission to hospital. A further report of 53 cases of formic acid ingestion included 15 fatalities.[2]

1. Naik RB, *et al.* Ingestion of formic acid-containing agents — report of three fatal cases. *Postgrad Med J* 1980; 56: 451–6.
2. Rajan N, *et al.* Formic acid poisoning with suicidal intent: a report of 53 cases. *Postgrad Med J* 1985; 61: 35–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Acimont; Berggeist; *Ital.*: Rubjovit; *Mex.*: Aminoyodarsencal; *Switz.*: Portalis; *Ukr.*: Medichronal (Медихронал).

Homoeopathic Preparations. *Austria*: Apozema Allium Cepa compositum; *Canad.*: Adrisin†; Cutisitum†; *Fr.*: Rhus Toxicodendron Compose; *Ger.*: Acirufan; Allergie-Injektopas; Allergo-Loges; Desarell; Formasan; Formidium; Formisoton; Heweformica; metablarex; Pascallerg; Presselin All; Regasinum antallergicum; Rufebran rheumo†; *Neth.*: Geovita; Habifac.

Fosfocreatinine *(rINN)*

Fosfocreatinina; Fosfocréatinine; Fosfocreatininum; Phosphocreatinine; Фосфокреатинин.
(1-Methyl-4-oxo-2-imidazolidinylidene)phosphoramidic acid.
$C_4H_8N_3O_4P$=193.1
CAS — 5786-71-0 (fosfocreatinine); 19604-05-8 (fosfocreatinine sodium).
UNII — RG2371KXDE.

Profile

Fosfocreatinine or fosfocreatinine sodium has been used in muscle disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Fosfructose Trisodium *(USAN, rINNM)*

CPC-111; Fosfructosa trisódica; Fosfructose Trisodique; Fosfructosum Trinatricum; Sodium Fructose-1,6-diphosphate; Тринатрий Фосфруктоза.
D-Fructose 1,6-bis(dihydrogen phosphate) trisodium octahydrate.
$C_6H_{11}Na_3O_{12}P_2.8H_2O$=550.2
CAS — 488-69-7 (fosfructose); 6055-82-9 (fosfructose calcium); 38099-82-0 (fosfructose trisodium); 81028-91-3 (fosfructose trisodium octahydrate).
ATC — C01EB07.
UNII — 463VBZ2YVD.

Profile

Fosfructose is a metabolic intermediate. It is used as the trisodium salt as a source of phosphate in deficiency states and in total parenteral nutrition, and has also been used to protect against ischaemic tissue damage. Fosfructose calcium has also been promoted for a variety of disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bo Wei He (博维赫); Esafosfina (爱赛福); Fodi (佛迪); Luo Pu Xin (洛普欣); Ruianji (瑞安吉); Wei Sai Xin (威赛欣); *Hong Kong*: Esafosfina; *Ital.*: Esafosfina; FDP; *Thai.*: Esafosfina†.

Multi-ingredient Preparations. *Hong Kong*: Esafosfina Glutammica.

Frankincense

Encens; Franchincenso; Kadidło; Kamanyang; Olibaanihartsi; Oliban; Olibano; Olibanum; Røgelse; Ru Xiang; Tamjan; Tămâie; Tus; Uunsi; Uvumba; Virak; Weihrauch; Лаban; Тамян.
CAS — 8016-36-2 (frankincense oil).
ATC Herb — HA03AW5005 (Boswellia sacra: resin); *HD03WA5001* (Boswellia sacra: resin); *HM01AW5004* (Boswellia sacra: resin).
UNII — R9XLF1R1WM.

NOTE. Distinguish from Indian Frankincense, below.

Profile

Frankincense is the aromatic gum resin of *Boswellia sacra* (*B. carteri*) (Burseraceae) or other species of *Boswellia*. It is used in incense and as a fumigant.

Frankincense (ru xiang) is also used in Chinese medicine. Frankincense oil is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Painease; Restorativ Glucosamine Muscle and Joint; *Fr.*: Capsaine; Tigre de Chine; *Philipp.*: BSI Medicated Plaster.

Homoeopathic Preparations. *Canad.*: Voxpax†; *Fr.*: Voxpax.

Indian Frankincense

Encens Indien; Indian Olibanum; Olibanum indicum; Salai Guggal; Weihrauch, Indischer.
UNII — 4PW41QCO2M.

NOTE. Indian frankincense is obtained from *Boswellia serrata* and should be distinguished from Frankincense (above) obtained from other species of *Boswellia*.

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

Ph. Eur. 8: (Indian Frankincense). Air-dried gum-resin exudate, obtained by incision in the stem or branches of *Boswellia serrata*. It contains a minimum of 1.0% of 11-keto-β-boswellic acid ($C_{30}H_{46}O_4$ = 470.7) and a minimum of 1.0% of acetyl-11-keto-β-boswellic acid ($C_{32}H_{48}O_5$ = 512.7) calculated with reference to the dried drug.

USP 36: (Boswellia Serrata). The oleogum resin obtained by incision or produced by spontaneous exudation from the stem and branches of *Boswellia serrata* (Burseraceae). It contains not less than 1% of the keto-derivatives of β-boswellic acid calculated on the dried basis, as the sum of 11-keto-β-boswellic acid and 3-acetyl-11-keto-β-boswellic acid. Store at a temperature between 8 degrees and 15 degrees. Protect from light and moisture.

Profile

Indian frankincense is the gum resin of *Boswellia serrata* (*B. glabra*) (Burseraceae). It has anti-inflammatory activity and is included in herbal preparations for musculoskeletal and joint disorders. It is also under investigation for use in inflammatory bowel disease and asthma. Boswellic acids extracted from the gum resin of *B. serrata* have also been tried for their anti-inflammatory actions in similar disorders.

References

1. Anonymous. *Boswellia serrata. Altern Med Rev* 2008; 13: 165–7.
2. Ernst E. Frankincense: systematic review. *BMJ* 2008; 337: a2813. Available at: http://www.bmj.com/cgi/reprint/337/dec17_2/a2813 (accessed 07/04/10)

Anti-inflammatory use. References to the use of Indian frankincense for its anti-inflammatory action.

1. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with ulcerative colitis. *Eur J Med Res* 1997; 2: 37–43.
2. Gupta I, *et al.* Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res* 1998; 3: 511–14.
3. Gupta I, *et al.* Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001; 67: 391–5.
4. Ammon HPT. Boswellic acids in chronic inflammatory diseases. *Planta Med* 2006; 72: 1100–16.
5. Abdel-Tawab M, *et al. Boswellia serrata*: an overall assessment of *in vitro*, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet* 2011; 50: 349–69.

OSTEOARTHRITIS. Indian frankincense has been used in the treatment of osteoarthritis of the knee and an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that it was safe and possibly effective in reducing pain and problems associated with walking and other daily activities, and that this effect might last for a period of time after stopping treatment.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and

fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Vedica; *USA*: 5-Loxin.

Multi-ingredient Preparations. *Arg.*: Glucobefol†; *Austral.*: Boswellia Complex; Boswellia Compound; Full Motion; Joint Ease; Joint Mobility†; *Chile*: Ruboril AI; *Fr.*: Arthro; Prostaform; *India*: Arthrill Forte; Artrex; Cartigen; Jointil Orthopedic oil; Jointil; Mobijoint; Niltan; Nucart-OA; *Indon.*: Ositin; *Ital.*: Actires; Pitogenase; Reumafort; Valedol; *Malaysia*: Rumalaya; *Philipp.*: Arthrid; *Singapore*: Artrex; Muvease; *Turk.*: Ultimate; *UK*: NatraFlex; PainEaze; *Ukr.*: Артритозамин (Артритозамин).

Homoeopathic Preparations. *Ger.*: Olibanum RA.

Fructo-oligosaccharides

Oligofructans; Oligofructose; Polyfructoses.

Profile

Fructo-oligosaccharides are fructans, sugar polymers containing a chain of fructose units, with or without a glucose unit at the start. They may be classified in several ways, depending on the degree of polymerisation and the type of glycosidic linkage present. Inulin (p. 2534.3) is a long-chain linear fructan with mainly β2→1 linkages and is the main fructan found in plants. Fructo-oligosaccharides usually contain 3 to 10 fructose units and are obtained by partial hydrolysis of inulin or by synthesis from sucrose; the name oligofructose is sometimes used specifically for those produced from inulin.

Fructo-oligosaccharides are a form of dietary fibre and are also known to have a prebiotic effect, stimulating the growth of certain colonic bacteria. They are used as dietary supplements and have been given with probiotic organisms (see p. 2596.3) in the management of gastrointestinal disorders; they have also been used to improve the absorption of dietary minerals. Fructo-oligosaccharides are also used as low-calorie sweetening agents.

Reviews.

1. Kelly G. Inulin-type prebiotics—a review: part 1. *Altern Med Rev* 2008; 13: 315–29.
2. Kelly G. Inulin-type prebiotics—a review: part 2. *Altern Med Rev* 2009; 14: 36–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Singapore*: Protexin.

Multi-ingredient Preparations. *Braz.*: Control†; *Fr.*: Immunostim; Maxi-Flore; Transifine; *Hong Kong*: Protexin Balance+; Protexin Balance; Protexin Restore; Protexin Vitality; *India*: Bioform; Biota-P; Colonise; Darolac Plus; Eubioz; Favolife; Flora-SB; Florablend; Goodlac; Gutrite; Hiact-P; IMM-4; Immunorm; Laff; New Probiza; Og-Lac; PP Bio; PP Tage; *Indon.*: Apecur; Biofos†; Calix†; Calvitran; Curfos; Curvit CL; Dhavit; Mulsanol; Obical; Protexin; Protexin; Seltifort Gold; Synbio; Vistrum; Vitacur; Vitagrow; Vitamam 1; Vitamam 2; Vitamam 3; Xanda; *Israel*: Biolax Protect; Biolax†; Co-Biotic Kid; *Ital.*: Estilax; Fervidus; Lactomaior; Ramnoflor Plus; Relaxcol; *Malaysia*: Obical; *Mex.*: Pedialyte POS; *Philipp.*: Exofat; *Singapore*: Obical; Pro-4; Pro-Gut; *UK*: Beneflora; Culture Care.

Fucoidan

Fucoidin; Fucoidine; Nemacystus Mucilage; Фукоидан.
CAS — 9072-19-9.

Profile

Fucoidan is a sulfated polysaccharide, based mainly on L-fucose, that is extracted from brown seaweed. It is reported to have anticoagulant, antithrombotic, and antineoplastic activity and has been promoted for a wide-range of disorders and as a food supplement.

References.

1. Mourão PA. Use of sulfated fucans as anticoagulant and antithrombotic agents: future perspectives. *Curr Pharm Des* 2004; 10: 967–81.

Nomenclature. Fucans are a class of sulfated polysaccharides first isolated from marine algae. Their nomenclature can be somewhat varied and confusing. The original polysaccharide isolated from algae was termed fucoidin and this was later changed to fucoidan. These polysaccharides have also been found in marine invertebrates and improved analytical and separation techniques have allowed different types of sulfated polysaccharides to be identified. It has been suggested that the term sulfated fucan should be defined as a polysaccharide based mainly on sulfated L-fucoses, with less than 10% other monosaccharides.[1] This term has been applied to the sulfated fucans of marine invertebrates, whereas the term fucoidan has been used for fucans extracted from algae. Some define fucoidan as a sulfated polysaccharide of L-fucose and D-galactose extracted from brown seaweed although others have used this term for sulfated polysaccharide complexes having a content of L-fucose of only 60% or less. Other terms that have been coined for these compounds include fucansulfate and fucan sulfate.

1. Berteau O, Mulloy B. Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 2003; 13: 29R–40R.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Fucobac; Fucosa; Fucotrap; Fudan; Gafudan; Mozuku.

Fumitory

Conejillos; Erdrauchkraut; Fumaria; Fumariae Herba; Fumeterre; Zemědýmová nať; Ziele dymnicy; Дымянка Лекарственная; Дымовая Трава.
ATC Herb — HA05AW5009 (Fumaria officinalis: herb).
UNII — VH659J61ZL (Fumaria officinalis flowering top).

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

Ph. Eur. 8: (Fumitory). The whole or fragmented, dried aerial parts of *Fumaria officinalis* harvested in full bloom. It contains a minimum of 0.40% of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5$ = 353.4). Protect from light.

Profile

Fumitory comprises the dried or fresh flowering plant *Fumaria officinalis* (Papaveraceae) and is used in herbal medicine. It is an ingredient of preparations used mainly for gastrointestinal and biliary-tract disorders.

Homoeopathy

Fumitory has been used in homoeopathic medicines under the following names: Fumaria; Fumaria officinalis.

Irritable bowel syndrome. Neither fumitory nor Javanese turmeric (p. 2636.2) was effective in a study[1] in patients with irritable bowel syndrome.

1. Brinkhaus B, *et al.* Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. *Scand J Gastroenterol* 2005; 40: 936–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Bilobene; Oddibil; *Braz.*: Oddibil; *Fr.*: Oddibil; *Ger.*: Bilobene†; *Hung.*: Bilobene; *Pol.*: Amphochol†.

Multi-ingredient Preparations. *Austria*: Hepabene†; *Fr.*: Actibil†; Azema†; Bolcitol†; Boribel Tisane No 7†; Depuratif Parnel†; Depuratum; Schoum; Tisane de Sante†; *Hung.*: Fumago; Hepabene; Livfit; *Ital.*: Soluzione Schoum; *Pol.*: Boldovera; *Rus.*: Hepabene (Гепабене); *Spain*: Solucion Schoum; *UK*: Echinacea; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; Skin Cleansing; *Ukr.*: Hepabene (Гепабене).

Homoeopathic Preparations. *Austria*: Lymphomyosot; *Canad.*: Eczema; *Cz.*: Lymphomyosot; *Fr.*: Saponaria Compose; *Ger.*: Haut-Gastreu R60; Heweberberol; Lymphomyosot N; Lymphomyosot; *Hung.*: Lymphomyosot; *Rus.*: Psorilom (Псорилом); *S. Afr.*: Lymphomyosot; *Ukr.*: Lymphomyosot (Лімфомиозот); Lymphomyosot N (Лімфомиозот Н).

Gabexate Mesilate *(rNNM)*

Gabexate, Mésilate de; Gabexate Mesylate; Gabexati Mesilas; Gabexato, mesilato de; Mesilato de gabexato; Габексата Мезилат.
Ethyl 4-(6-guanidinohexanoyloxy)benzoate methanesulphonate.
$C_{16}H_{23}N_3O_4.CH_4SO_3$=417.5
CAS — 39492-01-8 (gabexate); 56974-61-9 (gabexate mesilate).
UNII — E3Q07L0649.

Pharmacopoeias. In *Jpn.*

Profile

Gabexate mesilate is a proteolytic enzyme inhibitor that has been used for the treatment of pancreatitis (p. 2580.2) in an initial dose of 100 to 300 mg daily given by intravenous infusion. The dose may be reduced, or a further 100 to 300 mg given on the same day, according to response. It has also been used for disseminated intravascular coagulation (p. 1126.1) in a dose of 20 to 39 mg/kg given as a continuous intravenous infusion over 24 hours. Hypersensitivity reactions including anaphylaxis have occurred.

References.

1. Messori A, *et al.* Effectiveness of gabexate mesilate in acute pancreatitis: a metaanalysis. *Dig Dis Sci* 1995; 40: 734–8.
2. Cavallini G, *et al.* Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. *N Engl J Med* 1996; 335: 919–23.
3. Matsukawa Y, *et al.* Anaphylaxis induced by gabexate mesylate. *BMJ* 1998; 317: 1563.
4. Ranucci M, *et al.* Gabexate mesilate and antithrombin III for intraoperative anticoagulation in heparin pretreated patients. *Perfusion* 1999; 14: 357–62.
5. Matsukawa Y, *et al.* Fatal cases of gabexate mesilate-induced anaphylaxis. *Int J Clin Pharmacol Res* 2002; 22: 81–3.
6. Masci E, *et al.* Comparison of two dosing regimens of gabexate in the prophylaxis of post-ERCP pancreatitis. *Am J Gastroenterol* 2003; 98: 2182–6.
7. Andriulli A, *et al.* Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. *Clin Gastroenterol Hepatol* 2004; 2: 713–18.
8. Hsu JT, *et al.* Efficacy of gabexate mesilate on disseminated intravascular coagulation as a complication of infection developing after abdominal surgery. *J Formos Med Assoc* 2004; 103: 678–84.
9. Rudin D, *et al.* Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. *J Gastroenterol Hepatol* 2007; 22: 977–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Foy; Gabesato; *Jpn*: Foy.

Galactan Sulfate

Galactan Polysulfate; Galactane Sulphate.

Profile

Galactans are polysaccharides composed of repeating galactose units and can consist of branched or unbranched chains in any linkages. Sulfated galactans are found in marine algae and other marine organisms and examples such as carrageenan (p. 2176.3) and agar (p. 2167.2) are used as gelling agents. Sulfated galactans have also been used in gastrointestinal disorders and some are under investigation for their antithrombotic properties.

Reviews.

1. Pomin VH, Mourão PAS. Structure, biology, evolution, and medical importance of sulfated fucans and galactans. *Glycobiology* 2008; 18: 1016–27.
2. Pomin VH. Structural and functional insights into sulfated galactans: a systematic review. *Glycoconj J* 2010; 27: 1–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Acidrine; *Chile*: Sinacid†; *Fr.*: Acidrine; *Indon.*: Acidrine; *Ital.*: Acidrine; *Turk.*: Acidrine.

Galactomannan

Galactomanà; Galactomannaan; D-Galacto-D-mannan; Galactomanniane; Галактоманнаны.
CAS — 11078-30-1.

Profile

Galactomannans are natural gums consisting of hydrocolloidal polysaccharides formed from polymers of galactose and mannose. They occur in the endosperms of various seeds, particularly legumes, and are a source of dietary fibre. They have thickening, gelling, and hydrating properties and are used as pharmaceutical excipients, food additives, and in cosmetics; they also have many industrial applications. Examples include guar gum (p. 475.1) and ceratonia (p. 2178.1); other plant sources include fenugreek (p. 2504.1) and tara (*Caesalpinia spinosa*, Fabaceae).

Galactomannans are also found in the cell walls of some fungi, including *Aspergillus*, and tests to detect galactomannans in the blood have been used in the diagnosis of aspergillosis (p. 563.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Glucoman; Sirmiogel.

Gall

Agallas de roble; Aleppo Galls; Blue Galls; Dubenka; Galla; Galläpfel; Galls; Noix de Galle; Nutgall; Чернильный Орешек.

Pharmacopoeias. In *Chin.*

Profile

Gall is the excrescences on the twigs of *Quercus infectoria* (Fagaceae), resulting from the stimulus given to the tissues

of the young twigs by the development of the larvae of the gall-wasp, *Adleria gallae-tinctoriae* (*Cynips gallae-tinctoriae*) (Cynipidae). It contains about 50 to 70% of gallotannic acid.

Gall is an astringent and has been used in ointments and suppositories for the treatment of haemorrhoids. It is a source of tannic acid (p. 2625.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Good Time; *Thai.*: Relief Mouth Ulcer; *Ukr.*: Entoban (Энтобан).

Homoeopathic Preparations. *Ger.*: Juv 110.

Galsulfase *(BAN, USAN, rINN)*

BM-102; Galsulfasa; Galsulfasum; recombinant human arylsulfatase B; rhASB; Гальсульфас.

N-Acetylgalactosamine 4-sulfatase.

CAS — 552858-79-4.

ATC — A16AB08.

ATC Vet — QA16AB08.

UNII — 59UA429E5G.

NOTE. The name Aryplase has been used as a trade mark for galsulfase.

Uses and Administration

Galsulfase is recombinant human *N*-acetylgalactosamine 4-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis VI (see below). Galsulfase is given by intravenous infusion in a dose of 1 mg/kg once a week. Galsulfase should be reconstituted to a final volume of 250 mL in sodium chloride 0.9% and given using an infusion pump. The initial infusion rate should be 6 mL/hour for the first hour, which may then be increased to 80 mL/hour if well tolerated. The total infusion time should be at least 4 hours to minimise the risk of infusion reactions, but may be extended to up to 20 hours, or interrupted, if necessary, in the event of infusion reactions. Patients weighing 20 kg and under may be susceptible to fluid overload and a smaller infusion volume of 100 mL should be considered, in which case, the infusion rate should be decreased accordingly so that the total infusion time is not less than 4 hours.

Administration in children. Licensed product information for galsulfase in the treatment of mucopolysaccharidosis VI notes that children under 5 years of age were not included in phase III studies but nevertheless considers that patients in this age group with severe disease should be treated with the doses outlined above.

Mucopolysaccharidosis VI. Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) is a rare progressive disorder characterised by inherited deficiency of the enzyme *N*-acetylgalactosamine 4-sulfatase, which is necessary to catalyse the hydrolysis of the sulfate moiety of the glycosaminoglycan, dermatan sulfate. This results in accumulation of dermatan sulfate in the lysosomes producing widespread irreversible cellular and tissue damage, and organ dysfunction. There is a rapidly advancing form of the disease that presents in the first year of life characterised by short stature, skeletal and joint deformities, dysmorphic facial features, upper airway obstruction requiring tracheostomy, and recurrent ear infections. There is also a more slowly advancing form that progresses over many decades. Both forms result in significant morbidity and functional problems with a reduced lifespan.[1]

Treatment is supportive and symptomatic involving many body systems; physical and occupational therapy is also necessary.[1] Haematopoietic stem-cell transplantation to supply the deficient enzyme is of benefit to some patients, although it is associated with significant morbidity and mortality.[1] Enzyme replacement therapy with galsulfase has been reported to confer benefit with an acceptable safety profile.[1,2]

1. Giugliani R, *et al.* Management guidelines for mucopolysaccharidosis VI. *Pediatrics* 2007; 120: 405–18.
2. Harmatz P, *et al.* Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human *N*-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr* 2006; 148: 533–9.

Adverse Effects, Treatment, and Precautions

Infusion reactions have been reported in over half of patients treated with galsulfase and common symptoms have included fever, chills, rigor, rash, and urticaria. Other reported symptoms have included abdominal pain, nausea, vomiting, headache, malaise, angioedema, joint pain, hypotension, dyspnoea, bronchospasm, retrosternal pain, and respiratory distress. Antihistamines and/or antipyretics may relieve symptoms of infusion reactions. A reduction in the rate of infusion to half the rate at which the reaction occurred should also be considered for mild or moderate reactions; for severe reactions, the infusion should be stopped until symptoms have subsided, and then restarted at one-half to one-quarter the rate at which the reaction occurred. Pre-treatment with antihistamines and/or antipyretics about 30 to 60 minutes before infusion is recommended to prevent reactions.

IgG antibodies to galsulfase develop in the majority of patients within the first 4 to 8 weeks of treatment, although the effect on long-term efficacy or safety is not clear.

References.

1. Kim KH, *et al.* Successful management of difficult infusion-associated reactions in a young patient with mucopolysaccharidosis type VI receiving recombinant human arylsulfatase B (galsulfase [Naglazyme]). Abstract: *Pediatrics* 2008; 121: 609. Full version: http://pediatrics.aappublications.org/cgi/content/full/121/3/e714 (accessed 01/05/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Naglazyme; *Cz.*: Naglazyme; *Denm.*: Naglazyme; *Fr.*: Naglazyme; *Ger.*: Naglazyme; *Gr.*: Naglazyme; *Irl.*: Naglazyme; *Israel*: Naglazyme; *Ital.*: Naglazyme; *Mex.*: Naglazyme; *Neth.*: Naglazyme; *Pol.*: Naglazyme; *Port.*: Naglazyme; *Rus.*: Naglazym (Наглазим); *Spain*: Naglazyme; *Swed.*: Naglazyme; *Switz.*: Naglazyme; *USA*: Naglazyme.

Gamma-aminobutyric Acid

Ácido aminobutírico; Ácido gamma-aminobutírico; Ácido piperidíco; Acidum Aminobutyricum Gamma; Aminobutyric Acid; GABA; Gamma-aminosmörsyra; Gamma-aminovoihappo; Piperidic Acid; γ-Aminobutírico, ácido; Гамма-аминобутировая Кислота.

4-Aminobutyric acid.

$C_4H_9NO_2$=103.1

CAS — 56-12-2.

ATC — N03AG03.

ATC Vet — QN03AG03.

UNII — 2ACZ6IPC6I.

Profile

Gamma-aminobutyric acid is a principal inhibitory neurotransmitter in the CNS. It has been claimed to be of value in cerebral disorders and to have an antihypertensive effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Gammar; *China*: An Luo (安罗); Chang Rui (常瑞); Ge Le Si Te (格勒斯特); Hui You (慧友); Kai Luo (凯络); Li Sheng Bei Fen (丽生贝芬); Lu Bi An (卢必安); Sheng Mai Fu (升迈福); Ti Ta Ding (替他宁); Tu Tu (图图); Tuo Tai (拓泰); Wei Ding (为丁); Xin Nuo Shu (欣诺舒); Yi An Fen (异安芬); Yu Hui Luo (亿辉洛); Zhu Zhong Xin (竹中欣); *Hong Kong*: Gammalon; *Rus.*: Aminalon (Аминалон); *Thai.*: Bainto; Gammalon†; *Ukr.*: Aminalon (Аминалон).

Multi-ingredient Preparations. *Arg.*: Butineuron; Cadencial Plus; *Braz.*: Complevit†; Gaballon; Gabax†; Organoneuro Cerebral; *Chile*: Actebral; Cebrocal; Gamalate B6; Gamavit B6; *Spain*: Gamalate B6; *Ukr.*: Gamalate B6 (Гамалате B6); Olatropil (Олатропил).

Gamolenic Acid *(BAN, rINN)*

Acide Gamolénique; Ácido gamolénico; Ácido γ-linolénico; Acidum Gamolenicum; Gamolénico, ácido; GLA; γ-Linolenic Acid; Гамоленовая Кислота.

(*Z,Z,Z*)-Octadeca-6,9,12-trienoic acid.

$C_{18}H_{30}O_2$=278.4

CAS — 506-26-3.

ATC — D11AX02.

ATC Vet — QD11AX02.

UNII — 78YC2MAX4Q.

Linoleic Acid

Kwas linolowy; Linoleico, ácido; Linolic Acid; Linolsäure; Линолевая Кислота.

(*Z,Z*)-Octadeca-9,12-dienoic acid.

$C_{18}H_{32}O_2$=280.5

CAS — 60-33-3.

UNII — 9KJL21T0QJ.

Uses and Administration

Gamolenic and linoleic acid are essential fatty acids of the omega-6 series that act as prostaglandin precursors. Endogenous gamolenic acid is derived from linoleic acid, which is present in many plant oils and is an essential constituent of the diet. The most widely-used source of these acids is evening primrose oil (see p. 2502.2). Gamolenic and linoleic acids have been used in skin disorders and mastalgia, and have been investigated in other disorders including multiple sclerosis, rheumatoid arthritis, and the premenstrual syndrome.

Preparations containing essential fatty acids (formerly known collectively as vitamin F), including arachidonic acid, linoleic acid, linolenic acid (α-linolenic acid, p. 1460.2), oleic acid, and their derivatives, have been used similarly. Conjugated linoleic acid (CLA), a mixture of isomers in which *cis*-9,*trans*-11-octadecadienoic acid and *trans*-10,*cis*-12-octadecadienoic acid predominate, has also been used.

Products containing gamolenic-acid rich plant oils are promoted in many countries as dietary supplements, often in combination with fish oils or other sources of omega-3 fatty acids (see p. 1460.1).

A derivative of gamolenic acid, lithium gamolenate, has been investigated in pancreatic cancer.

Eczema. Atopic eczema (p. 1684.1) may be due to a defect in essential fatty acid metabolism[1,2] and some beneficial symptomatic effects have been reported with evening primrose oil.[1,3] Meta-analysis of 9 studies involving 311 patients[4] has reported improvement in disease symptoms, especially itching, but a subsequent study in 123 patients found no therapeutic effect of evening primrose oil, alone or with fish oil.[5] Although the design and interpretation of this study has been criticised by the manufacturers of evening primrose oil,[6] the authors consider such criticism invalid,[7] and point out that an earlier large study yielded similar results.[8] No difference was found between placebo and evening primrose oil in a further study[9] in children with eczema, and there was also no effect on asthma symptoms in those patients suffering from both disorders. Studies[10,11] of borage oil (another source of gamolenic acid) also found no overall efficacy in adults or children with atopic eczema, although one study noted a suggestion of benefit in a subgroup of patients.[10] In a study[12] of a group of formula-fed infants with a high maternal familial risk of developing atopic eczema, borage oil supplementation did not prevent the expression of atopy, although it showed a tendency to alleviate the severity of the condition later in infancy.

Benefit has been reported in infants with seborrhoeic dermatitis from local application of borage oil.[13]

1. Wright S. Essential fatty acids and the skin. *Br J Dermatol* 1991; 125: 503–15.
2. Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. *Am J Clin Nutr* 2000; 71 (suppl): 367S–372S.
3. Rustin MHA. Dermatology. *Postgrad Med J* 1990; 66: 894–905.
4. Morse PF, *et al.* Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema: relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989; 121: 75–90.
5. Berth-Jones J, Graham-Brown RAC. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; 341: 1557–60. Correction. *ibid.*; 342: 564.
6. Shield MJ, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; 342: 377.
7. Berth-Jones J, *et al.* Essential fatty acid supplementation in atopic dermatitis. *Lancet* 1993; 342: 377–8. Correction. *ibid.*; 752.
8. Bamford JTM, *et al.* Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1985; 13: 959–65.
9. Hederos C-A, Berg A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. *Arch Dis Child* 1996; 75: 494–7.
10. Henz BM, *et al.* Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999; 140: 685–8.
11. Takwale A, *et al.* Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003; 327: 1385–7.
12. van Gool CJ, *et al.* γ-Linolenic acid supplementation for prophylaxis of atopic dermatitis—a randomized controlled trial in infants at high familial risk. *Am J Clin Nutr* 2003; 77: 943–51.
13. Tollesson A, Frithz A. Borage oil, an effective new treatment for infantile seborrhoeic dermatitis. *Br J Dermatol* 1993; 129: 95.

Mastalgia. Gamolenic acid (usually given in the form of evening primrose oil) has fewer adverse effects than drugs such as danazol or bromocriptine and has been preferred for mastalgia (p. 2265.1), especially in patients with less severe symptoms or those who require prolonged or repeated treatment. However, there is no clear evidence of efficacy.

Multiple sclerosis. There is some evidence that modifying the intake of dietary fats and supplementing the diet with omega-6 polyunsaturated fatty acids, such as linoleic acid, could influence the clinical course of multiple sclerosis (p. 996.3) and many patients practise dietary modification, including taking evening primrose oil. One study[1] has shown a reduction in severity and duration of relapse in patients taking linoleic acid supplements (as sunflower oil), and another[2] has reported benefit in patients who limited their intake of dietary saturated fatty acids and supplemented their diet with polyunsaturated fatty acids. A systematic review[3] of the relationship between dietary interventions (including linoleic acid supplements) and

MS concluded that there was insufficient evidence to determine their benefits or risks.

1. Millar JHD, *et al.* Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *BMJ* 1973; 1: 765–8.
2. Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 1990; 336: 37–9.
3. 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).

Premenstrual syndrome. Progressive improvement in premenstrual syndrome (p. 2272.3) was reported over 5 cycles in an open pilot study in 19 patients receiving evening primrose oil.[1] However, subsequent results have not shown any benefit.[2-4] Evening primrose oil has been considered for cyclical mastalgia (see p. 2509.3).

1. Larsson B, *et al.* Evening primrose oil in the treatment of premenstrual syndrome: a pilot study. *Curr Ther Res* 1989; 46: 58–63.
2. Khoo SK, *et al.* Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990; 153: 189–92.
3. Collins A, *et al.* Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol* 1993; 81: 93–8.
4. Budeiri DJ, *et al.* Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996; 17: 60–8.

Rheumatoid arthritis. Patients with rheumatoid arthritis (p. 13.2) taking NSAIDs have shown subjective improvement after 12 months of treatment with evening primrose oil, with or without fish oil, when compared with placebo.[1] A clinically important reduction in signs and symptoms of disease activity has also been seen in patients treated with gamolenic acid in the form of borage oil.[2] During treatment with evening primrose oil patients with rheumatoid arthritis have increased plasma concentrations of gamolenic, dihomo-gamma-linolenic, and arachidonic acids, and decreased plasma concentrations of oleic and eicosapentaenoic acids and apolipoprotein B.[3] The increase in plasma-arachidonic acid and decrease in eicosapentaenoic acid might be unfavourable in such patients, since arachidonic acid is the precursor of inflammatory prostaglandins and eicosapentaenoic acid may have an anti-inflammatory role. However, a systematic review[4] of these and other studies concluded that there does appear to be some potential benefit for the use of gamolenic acid in rheumatoid arthritis, although optimum dosage and duration of treatment is unknown.

1. Belch JJF, *et al.* Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988; 47: 96–104.
2. Leventhal LJ, *et al.* Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993; 119: 867–73.
3. Jäntti J, *et al.* Evening primrose oil in rheumatoid arthritis: changes in serum lipids and fatty acids. *Ann Rheum Dis* 1989; 48: 124–7.
4. Little CV, Parsons T. Herbal therapy for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2000 (accessed 23/05/06).

Adverse Effects and Precautions

Gamolenic and linoleic acids from evening primrose oil, and presumably other sources, can produce minor gastrointestinal disturbances and headache. They can precipitate symptoms of undiagnosed temporal lobe epilepsy, and should be used with caution in patients with a history of epilepsy or those taking epileptogenic drugs, in particular phenothiazines. Hypersensitivity reactions may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: CLA 500; Metabolic CLA; *Ger.*: Sanyrene; *Hong Kong*: Welsan Dual Shower Oil; *India*: GLA; Linocid; *Ital.*: Triene; Vitef; *Pol.*: Dermovit F; Linola; Linomag; *UK*: Super GLA.

Multi-ingredient Preparations. *Arg.*: Atomo Ordenador; Dial-ND; Epasterol; KW; Macbirs; Omeganorm†; Proavenal Omegatopic; Quelodin F; Revi-Atlas; *Austria*: Mamellin; Sulgan 99; *Braz.*: Glavit†; Oleo de Primula; *Canad.*: Bionagre plus E†; *Chile*: Delgadol Slim; Effaclar H; Infor; Proaven; Revi-Atlas; Ureadin Pediatrics; *Cz.*: Linola-Fett; Linola; *Fr.*: Sun Vue; Trimada; *Ger.*: Hydro Cordes; Linola-Fett; Linola; Lipo Cordes; Unguentacid†; *Gr.*: Striafissan; *Hong Kong*: Doctor's Choice Multivitamins and Minerals for Eyes; Eye Q; Welsan Lipocream; *Hung.*: Linola; *India*: Accept; Alphaneuron; Cobal Plus; Combinac; Diptase; Eladerm; GLA-M; GMab Plus; Nimulid Nugel; Onerve; *Ital.*: Dermagan; Derman-Oil; Dermana Crema; Dermana Pasta; Efagel; Esterol; Medilar; Neuralfa; Osteolip; Pasta Dicofarm; Tiofort; Topialyse; Trofinerv Antiox; *Malaysia*: Pharmaton†; *Mex.*: Nutrem; *NZ*: Efamast†; Efanatal; *Philipp.*: K-A Plus; Pharmaton; *Port.*: Geriso; Thiospot; *Singapore*: Eye Q Equazen†; Manhac; *Spain*: Dermisone Epitelizante†; Doctofril Antiinflamat†; Nutracel; Vitamina P99 Topica†; *Switz.*: Linola gras; Linola migras†; Linola; Sulgan N; Vitafissan N; *UK*: Lacrima.

Gangliosides

Gangliósidos; Ганглиозиды.

Profile

Gangliosides are endogenous substances present in mammalian cell membranes, especially in the cortex of the brain. They are glycosphingolipids composed of a hydrophilic oligosaccharide chain, characterised by sialic acid residues, attached to a lipophilic moiety. The four major gangliosides found in the mammalian brain are referred to as G_{M1}, G_{D1a}, G_{D1b}, and G_{T1b}.

Experimental studies have reported that gangliosides may have a neuroprotective effect on the CNS and peripheral nervous system. Preparations of gangliosides from bovine brain have been given for peripheral neuropathies and cerebrovascular disorders and their role in spinal cord injury has also been investigated. The modified ganglioside siagoside has been studied in patients with Parkinson's disease.

Concern was expressed about the development of Guillain-Barré syndrome and other motor neurone disorders in some patients, and it was suggested that gangliosides were contra-indicated in Guillain-Barré syndrome and all auto-immune disorders. Subsequently these concerns over safety and doubts about efficacy led to the withdrawal of ganglioside preparations in many countries.

References.

1. Geisler FH, *et al.* Recovery of motor function after spinal-cord injury—a randomized, placebo-controlled trial with GM-1 ganglioside. *N Engl J Med* 1991; 324: 1829–38.
2. Raschetti R, *et al.* Guillain-Barré syndrome and ganglioside therapy in Italy. *Lancet* 1992; 340: 60.
3. Figueras A, *et al.* Bovine gangliosides and acute motor polyneuropathy. *BMJ* 1992; 305: 1330–1.
4. Roberts JW, *et al.* Iatrogenic hyperlipidaemia with GM-1 ganglioside. *Lancet* 1993; 342: 115.
5. Landi G, *et al.* Guillain-Barré syndrome after exogenous gangliosides in Italy. *BMJ* 1993; 307: 1463–4.
6. Nobile-Orazio E, *et al.* Gangliosides: their role in clinical neurology. *Drugs* 1994; 47: 576–85.
7. Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2001 (accessed 23/05/06).
8. Fredman P, *et al.* Gangliosides as therapeutic targets for cancer. *BioDrugs* 2003; 17: 155–67.
9. Govoni V, *et al.* Is there a decrease in Guillain-Barré syndrome incidence after bovine ganglioside withdrawal in Italy? A population-based study in the Local Health District of Ferrara, Italy. *J Neurol Sci* 2003; 216: 99–103.
10. Chinnock P, Roberts I. Gangliosides for acute spinal cord injury. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2005 (accessed 23/05/06).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Sinaxial; Sygen; *China*: Shen Jie (申捷); Sygen (富塑杰); *Gr.*: Sygen; *Singapore*: Cronassial; Sygen.

Garcinia Cambogia

Brindall Berry; Brindleberry; Malabar Tamarind; Гарциния Камбоджа.

CAS — 90045-23-1 (Garcinia cambogia extract).

UNII — BLL74KMB5 (Garcinia cambogia); D0QJ8UQVR (Garcinia cambogia fruit); 253B88SCZ4 (Garcinia cambogia fruit rind).

Pharmacopoeias. *US* includes Garcinia Cambogia as well as a powdered form. There is also a standard for a powdered hydroxycitrate extract which may be prepared from either *Garcinia cambogia* or *G. indica*.

USP 36: (Garcinia Cambogia). The dried pericarp of the fruits of *Garcinia gummi-gutta* (*G. cambogia*) (Clusiaceae). It contains not less than 12% of the sum of (-)-hydroxycitric acid and (-)-hydroxycitric acid lactone, on the dried basis. Protect from light and moisture.

Profile

Extracts of Garcinia cambogia (*Garcinia gummi-gutta*, Clusiaceae) are a source of hydroxycitric acid and are included in preparations for the treatment of obesity.

Several species of *Garcinia* are used in traditional medicine, as a food source, and as a source of the pigment gamboge.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Terocaps.

Multi-ingredient Preparations. *Arg.*: Adel; Desgras Burner Fat; Garcinia + Fucus; Garcinia Cambogia Compuesta; Garcinol Max; Indian Health - Garcinia; Mermelax; Metabolic Reductase; Reducliet; Ripped Max; Silueta Plus†; *Austral.*: 3B Beer Belly Buster†; Citri Slim+Trim†; Metabolift Fat Burner; *India*: Obedeuce; *Indon.*: Betaslim; Combes†; Vitaslim; *Ital.*: Altadrine; Fibrovit; Snell Cell†; *Mex.*: Slim-D†; *Singapore*: Chitosano; Mincifit Body Shaper; *Ukr.*: Liponorm (Липонорм); Stifimo (Стифимол).

Garlic

Aglio; Ail; Ail, poudre d' (garlic powder); Ajo; Allii sativi bulbi pulvis (garlic powder); Allium; Allium Sativum; Cibule česneku setého práškovaná (garlic powder); Fokhagymapor (garlic powder); Knoblauch; Valkosipuli; Vitlök; Česnaku milteliai (garlic powder); Чеснок.

CAS — 8008-99-9 (garlic extract).

ATC Herb — HJ01WB5002 (Allium sativum: bulb); HJ01WA5001 (Allium sativum: bulb); HC10AW5002 (Allium sativum: bulb).

UNII — II1F21WT8O3 (Allium sativum); V1V998DC17 (Allium sativum bulb).

Pharmacopoeias. In *US*, which also includes Garlic Fluidextract, Powdered Garlic, and Powdered Garlic Extract. *Eur.* (see p. vii) includes Garlic Powder.

Eur. also includes Garlic for Homoeopathic Preparations.

Ph. Eur. 8: (Garlic Powder). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65 degrees, and powdered. It contains not less than 0.45% of allicin, calculated with reference to the dried drug. It is a light yellowish powder. Protect from light.

Ph. Eur. 8: (Garlic for Homoeopathic Preparations). The fresh bulb of *Allium sativum*. Store in airtight containers. Protect from light.

USP 36: (Garlic). The fresh or dried compound bulbs of *Allium sativum* (Liliaceae). It contains not less than 0.5% of alliin and not less than 0.2% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees. Protect from light.

USP 36: (Powdered Garlic). It is produced from garlic that has been cut, freeze-dried or dried at a temperature not exceeding 65 degrees, and powdered. It contains not less than 0.3% of alliin and not less than 0.1% of γ-glutamyl-(*S*)-allyl-L-cysteine, calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees. Protect from light.

Uses and Administration

The constituents of garlic include alliin, allicin, diallyl disulfide, and ajoene. It has traditionally been reported to have expectorant, diaphoretic, disinfectant, and diuretic properties. More recently, it has been investigated for antimicrobial, antihypertensive, lipid-lowering, fibrinolytic, antiplatelet, and cancer protective effects. Garlic oil has also been used.

Homoeopathy

Garlic has been used in homoeopathic medicines under the following names: Allium sativum; Allium sat; All. sat.

References.

1. Kleijnen J, *et al.* Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; 28: 535–44.
2. Mansell P, Reckless JPD. Garlic. *BMJ* 1991; 303: 379–80.
3. McElnay JC, Po ALW. Garlic. *Pharm J* 1991; 246: 324–6.
4. Kiesewetter H, *et al.* Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *Eur J Clin Pharmacol* 1993; 45: 333–6.
5. Deshpande RG, *et al.* Inhibition of Mycobacterium avium complex isolates from AIDS patients by garlic (Allium sativum). *J Antimicrob Chemother* 1993; 32: 623–6.
6. Dorant E, *et al.* Garlic and its significance for the prevention of cancer in humans: a critical review. *Br J Cancer* 1993; 67: 424–9.
7. WHO. Bulbus Alii Sativi. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/4.html (accessed 04/02/10).
8. Ackermann RT, *et al.* Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med* 2001; 161: 813–24.
9. Tattelman E. Health effects of garlic. *Am Fam Physician* 2005; 72: 103–6.
10. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. *J Nutr* 2006; 136 (suppl): 736S–740S.
11. Reinhart KM, *et al.* Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother* 2008; 42: 1766–71.

Common cold. Although garlic is used as a remedy for the common cold because it is believed to have antibacterial and antiviral properties, a systematic review[1] found insufficient evidence of benefit from clinical studies and that claims of efficacy have come from poor quality evidence.

1. Lissiman E, *et al.* Garlic for the common cold. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2009 (accessed 02/12/09).

Hyperlipidaemia. Garlic has been widely promoted for use in the treatment of hyperlipidaemia (p. 1248.1). Several early placebo-controlled studies[1,2] and meta-analyses[3,4] showed that garlic significantly decreased total serum-cholesterol concentrations. However, more recent data suggest that the effect is at best modest[5] or that there

is no significant difference[4-9] when compared with placebo.

1. Jain AK, *et al.* Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med* 1993; **94:** 632–5.
2. Kemzeimann R, Kade P. Limitation of the deterioration of lipid parameters by a standardized garlic-ginkgo combination product: a multicenter placebo-controlled double-blind study. *Arzneimittelforschung* 1993; **43:** 978–81.
3. Warshafsky S, *et al.* Effect of garlic on total serum cholesterol: a meta-analysis. *Ann Intern Med* 1993; **119:** 599–605.
4. Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. *J R Coll Physicians Lond* 1994; **28:** 39–45.
5. Stevinson C, *et al.* Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. *Ann Intern Med* 2000; **133:** 420–9.
6. Neil HAW, *et al.* Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and a meta-analysis. *J R Coll Physicians Lond* 1996; **30:** 329–34.
7. Berthold HK, *et al.* Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *JAMA* 1998; **279:** 1900–2.
8. Isaacsohn JL, *et al.* Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med* 1998; **158:** 1189–94.
9. Gardner CD, *et al.* Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. *Arch Intern Med* 2007; **167:** 346–53.

Adverse Effects

Effects on the skin. Reports of burns or skin lesions after topical application of garlic to children,[1,2] and to adults,[3,4] including self-inflicted injury.[5]

1. Garty B-Z. Garlic burns. *Pediatrics* 1993; **91:** 658–9.
2. Canduela V, *et al.* Garlic: always good for the health? *Br J Dermatol* 1995; **132:** 161–2.
3. Farrell AM, Staughton RCD. Garlic burns mimicking herpes zoster. *Lancet* 1996; **347:** 1195.
4. Eming SA, *et al.* Severe toxic contact dermatitis caused by garlic. *Br J Dermatol* 1999; **141:** 391–2.
5. Lachter J, *et al.* Garlic: a way out of work. *Mil Med* 2003; **168:** 499–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ajo Vital; Ajomast; Alliocaps; *Austral.*: Garlix†; *Austria*: Kwai; *Fr.*: Inod'ail; *Ger.*: Kwai; Sapec; Strongus†; *Hung.*: Allidex; *India*: Garlee; Garlic Pearls; *Ital.*: Kwai; *Malaysia*: Kyolic; *Pol.*: Allovital†; Alitol; Gerlacaps; *Swed.*: Kyolic; *Thai.*: Cilrag; *Turk.*: Cirkulin; *UK*: Garlimega; Kwai; Kyolic; *Ukr.*: Allocholum (Аллохол); Herbion Allium (Гербион Аллиум); Revital Garlic Pearls (Ревайтл Чесночные Жемчужины)†.

Multi-ingredient Preparations. *Arg.*: Aglio†; Ajo 1000 + C; Ajo Forte†; Ajo Mas Vitamina C; Ajolip; Exail; Varisedan; *Austral.*: Airborne Immunity; ChelaCo; Daily Plus Max†; Echinacea Plus Garlix; Garlic Allium Complex; Garlic and Horseradish + C Complex†; Gartech†; Lemsip First Signs Cold & Flu Day + Night; Lemsip First Signs Cold & Flu; Menevit; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Odourless Garlic; Olive Leaf Plus; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; *Austria*: Rutiviscal; *Canad.*: Defense; Kyolic 101†; Kyolic 102†; Para-Gone; *Fr.*: Arterase; Dida; ProstaSecurA; *Ger.*: Ilja Rogoff; Klosterfrau Aktiv†; Lipidavit†; *Hong Kong*: Bio-Kult Candea; Cardioace; Doctor's Choice Multivitamins and Minerals for Eyes; Wellman; *Hung.*: Allithera; Antisklerin; Sanhelios 333; *India*: Arthrill; Full-24; Garlill; GGG-24; Lactare; Multivite Gold; *Indon.*: Garlic-Plus; Imox; Naturlesterol; Resvica†; Sotens†; *Ital.*: Angiovein; Artedin; Valcap; *Malaysia*: Circarol; *Mex.*: Hepafol-F; Supravital; *Philipp.*: Circulan; Nutrotal; *Pol.*: Alchinal; Alliofil; Alliorut†; Cepasmel; Cepastil; Doppelherz Vital Kapseln†; Klosterfrau Aktiv; *Rus.*: Wellman (Велмен); *Singapore*: Bio-Kult Candea; *Switz.*: Allium Plus†; Arterosan Plus†; Keli-med; *UK*: Allerclear; Antifect; Cardioace; Clogar; Fishogar; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Liqufruta Garlic Cough Medicine; Super Antioxidant Plus; *Ukr.*: Gold Ray (Голд Рей); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Vitokan (Витокан); Wellman (Велмен); *USA*: Cardiopress; Fitness Tabs for Men; Fitness Tabs for Women; Immunicare.

Homoeopathic Preparations. *Canad.*: Mucan; *Chile*: Flucoccinum; *Ger.*: Nux Vomica N Oligoplex; RauwolfiaViscomp; *Switz.*: Regenaplex Nr 38b; Regenaplex Nr. 50b.

Pharmacopoeial Preparations
USP 36: Garlic Delayed-Release Tablets.

Gavestinel *(BAN, USAN, rINN)*

Gavestinelum; GV-150526X; Гавестинел.
4,6-Dichloro-3-[(*E*)-2-(phenylcarbamoyl)vinyl]indole-2-carboxylic acid.
$C_{18}H_{12}Cl_2N_2O_3$=375.2
CAS — 153436-22-7.
UNII — 318X4QY113.

Profile

Gavestinel is a glycine antagonist that has been investigated as a neuroprotectant in stroke.

Stroke. Gavestinel has been tried for its supposed neuroprotective properties in acute stroke, but two major multicentre, randomised controlled studies have failed to show any benefit over placebo in acute ischaemic stroke.[1,2] Analysis of the data from these two studies in patients with primary intracerebral haemorrhage found no benefit of gavestinel in this subgroup either.[3]

1. Lees KR, *et al.* Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. *Lancet* 2000; **355:** 1949–54.
2. Sacco RL, *et al.* Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. *JAMA* 2001; **285:** 1719–28.
3. Haley EC, *et al.* Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. *Stroke* 2005; **36:** 1006–10.

Gelsemium

Gelsemium Root; Jessamine; Madreselva; Raíz del gelsemio; Raíz del jazmín amarillo; Yellow Jasmine Root; Корень Желтого Жасмина.
CAS — 509-15-9 (gelsemine).
UNII — 639KR60Q1Q.

Profile

Gelsemium consists of the dried rhizome and roots of *Gelsemium sempervirens* (Loganiaceae). It contains toxic indole alkaloids including gelsemine ($C_{20}H_{22}N_2O_2$ = 322.4). It depresses the CNS and has been used mainly in neuralgic conditions, particularly trigeminal neuralgia and migraine.

Homoeopathy

Gelsemium has been used in homoeopathic medicines under the following names: Gelsemium sempervirens; Gels.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Coquelusedal Nourrissons; Coquelusedal Paracetamol Nourrissons†; Coquelusedal Paracetamol; Coquelusedal; *Port.*: Cephyl†.

Homoeopathic Preparations. *Austral.*: Childrens Cold and Flu Relief; Childrens Sleep; Hangover Relief; Pain & Fever Relief; Sleep & Insomnia Relief; *Austria*: Aconitum Med Complex; Cranagil; Globuli gegen Kopfschmerzen; Metavirulent; Migrenopas†; Nisylen†; Rytmopasc; Spigelon; *Canad.*: Bioactiv N†; C-Plus; Calsom†; Cold Tablets with Zinc†; Complete Flu Care 4 Kids†; Coryzalia; Echinacea Compositum; Hea Complex†; Headache & Migraine L77; Herpes Soothing Cream; Homeo-Form CA†; Homeo-Form M†; Hyalgesic HP†; Hylands Flu; Hylands Formula CZ; Hylands Formula F; Hylands Headache; Hylands PMS; Hylaprin; Ikoplex 12†; Ivernax; L52 Cough & Cold; Lopraxt; Mental Alertness; Nervita; Nixotinex; Quietude; Spascupreel; Spigelon†; *Chile*: Allium Compuesto; Bioactiv N; Drosemiel; Flucoccinum; Grippakit; Ikoplex No 12; Lumboplex; TBR/X; *Cz.*: Coryzalia; Gelsemium-Homaccord; Lehnigrip†; Paragrippe; Sedalia; Spascupreel S†; *Fr.*: Acidum Phosphoricum Complexe No 5; Acidum Phosphoricum Compose†; Anxietum; Boripharm No 31; Boripharm No 3; Coryzalia; Gelsemium Complexe No 70; grippe†; L 52; Paragrippe; Phapax; Quietude; Ranunculus Complexe No 79; Slipeol†; Zenalia; Zincum Cyanidum Complexe No 101†; *Ger.*: A-Bomin; Anovin; Antimigren; Biodolor; Cefagrippin†; Cefanalgin†; Cefaneuro; Cefatropin N†; Chirofossat; Cranio-cyl Ho-Len-Complex; Curare comp; DolorA; dysto-loges N; dysto-loges S; Echinacea comp; Febrocyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Gelsemium N Oligoplex; Grippe-Gastreu S R6; Gripps; HanoFemin; HanoToxin M; Hanotoxin M; Infekt-Komplex L Ho-Fu-Complex; Infi-Echinacea; Infi-Symphytum; Infigripp; Influvit; Jowidarmin; metavirulent; Migrane Hevert†; Migrane Hevert; Migrane-Gastreu R16; Neuralgie-Injektopas SL; Neuro-Do; Neuro-Ginsan N; Neuroselect; Nisylen; Pascallerg; Pflugerplex Gelsemium; Rephalgin N; Rytmopasc; Schworotox A; Sedaselect; Spascupreel; Wiedimmun; Zahnungstropfen Escatitona; Zerosorin SN†; *Hung.*: Coryzalia; Gelsemium-Homaccord; Spascupreel; Spigelon; *Neth.*: Arnilite; Cephalite; Coryzalia; Grippe-Gastreu R6; Homeocare Nervo; Hyperilite; Kind 0-6 Kindtherm; Kind 0-6 Nisykind; Kruidvat Homeopathie Influ-complex†; Mullimen H; Nervofleur; Nisyleen; Paragrippe†; Quietude†; Spascupreel H; *Port.*: Coryzalia; Paragrippe; *Rus.*: Aurum Plus (Аурум-Плюс); Briacon (Бриакон); Coryzalia (Коризалия); Crataegus-Plus (Крателгус-Плюс); Influcid (Инфлюцид); Mirticam (Миртикам); *Switz.*: Coryzalia; Influaforce†; metavirulent; Quietude; Regenaplex Nr. 3; Spigelon; *UK*: Coldenza; *Ukr.*: Capadol (Кападол); Coryzalia (Коризалия); Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†; Influcid (Инфлюцид); *USA*: Preferred Remedies Cold & Flu.

Gene Therapy

Terapéutica génica; Генотерапия.

Profile

Gene therapy is a product of the increasing knowledge of genetic function and the availability of methods to examine and manipulate the genome. Exogenous genetic material, which may be synthetic or recombinant, nucleic acids (p. 2573.1), is introduced into somatic cells (transfection) in such a way that the cells are able to express the products of the new genes. It may be used for therapeutic, prophylactic, or diagnostic purposes. Gene therapy should be distinguished from the use of products derived from organisms (usually micro-organisms) whose genome has been manipulated by similar recombinant DNA technology, for example the use of recombinant cytokines (p. 2491.2), monoclonal antibodies (p. 2561.1), or antisense products.

Gene therapy is under investigation in three main areas:
- the replacement of abnormal or defective genes in patients with inherited disease
- the alteration of the characteristics of cells to change their relative susceptibility to other therapies (for example by making haematopoietic stem cells more resistant to the adverse effects of antineoplastics, or by making tumour cells selectively express an enzyme that converts an otherwise non-toxic prodrug into a cytotoxic agent)
- for localised production of a biologically active substance that cannot be given directly or would have unacceptable effects if used systemically.

To date, all gene therapy in humans has been of differentiated somatic cells. Alteration of the human genome in a manner transmissible to offspring, either by treating the germ cells or the early embryo, is considered at present to pose insuperable ethical problems.

Various methods for delivery of genetic material have been investigated, none of which is yet completely satisfactory. These include biological vectors (e.g. viruses or plasmids) or stem cells that have been genetically modified, oncolytic viruses, nucleic acids, either naked plasmids or carried by delivery vehicles, and genetic vaccines. Antisense techniques to modify, correct, or silence aberrant genes are also being developed, as is RNA interference. Xenotransplantation of animal cells may also be an option. Removal of donor cells from the patient followed by *ex vivo* transfer of the new gene (by physical or viral methods) and return of the modified cells may be feasible for modifying haematopoietic stem cells. However, for most tissues, methods of *in vivo* transfer are required. Modified viruses rendered incapable of replicating have been widely studied as vectors for gene therapy. Retroviruses have the advantage that the DNA they carry is integrated into the host genome, resulting in permanent expression of the gene, but there has been some concern that they may disrupt existing genetic material with possibly oncogenic effect; in addition, their small size limits the size of gene that they can carry, and they are largely ineffective in infecting non-dividing cells. Adenoviruses are more stable and can infect non-dividing as well as dividing cells, but their genetic freight is not integrated into the chromosome and transmitted to the cell's progeny, and the gene products are therefore only expressed transiently; they are also highly immunogenic which limits repeated use. Some other viral types, including herpes simplex viruses, adeno-associated viruses, and lentiviruses, are also under investigation. Viruses with tropisms for a particular tissue may be useful in producing localised effects.

Chemical or physical methods for DNA delivery have been extensively investigated. Such methods include direct injection of DNA, the use of DNA complexes bound to a ligand which can be taken up by cells, formulation of DNA in liposomes which can fuse with cell membranes and allow the DNA to enter the cell, and more exotic methods such as 'gene guns', in which DNA-coated gold particles are fired into the cells. Although gene expression can be achieved after use of such methods, it is again transient because the new genetic material is not integrated with that of the host, and physical methods are currently less efficient and more limited in scope than viral ones.

Many clinical studies are being carried out. The first successful therapy was for severe combined immunodeficiency, a single-gene disorder due to deficiency of the enzyme adenosine deaminase. Transfection of the gene for this enzyme into the patient's T-cells *ex vivo* and re-infusion of the modified T-cells has been shown to produce substantial clinical improvement, although therapy must be repeated periodically because of the limited lifespan of the lymphocytes.

Studies in patients with cystic fibrosis have also shown some success, and several other single-gene disorders, including alpha$_1$ antitrypsin deficiency, Gaucher disease, the haemoglobinopathies and haemophilias, and Duchenne muscular dystrophy are being studied or have been proposed as possible candidates. Alipogene tiparvovec (p. 2434.2), a nonreplicating adeno-associated viral vector (AAV1) that carries a gene for lipoprotein lipase, is used for the treatment of familial lipoprotein lipase deficiency.

Gene therapy is also under investigation in various acquired diseases, particularly in the management of various types of cancer. Strategies being studied include modification of tumour cells either to increase their immunogenicity or to render them selectively sensitive to antineoplastics, transfection of tumour cells with tumour suppressor genes, and transfection of healthy cells to

produce cancer killing substances. Other disorders being studied clinically include HIV infection, rheumatoid arthritis, Parkinson's disease and atherosclerosis.

Some reviews and references concerning gene therapy are listed below. See also under the discussions of individual diseases for comments on gene therapy in the context of their conventional treatment.

1. Hu WS, Pathak VK. Design of retroviral vectors and helper cells for gene therapy. *Pharmacol Rev* 2000; 52: 493–511.
2. WHO. Gene transfer medicinal products. *WHO Drug Inf* 2002; 16: 275–82.
3. Tomanin R, Scarpa M. Why do we need new gene therapy viral vectors? Characteristics, limitations and future perspectives of viral vector transduction. *Curr Gene Ther* 2004; 4: 357–72.
4. DoH. Recommendations of the GTAC/CSM working party on retroviruses. Internet Document: May 2005. Available at: http://www.advisorybodies.doh.gov.uk/genetics/gtac/Finalrecommendations-June2005.pdf (accessed 11/02/08)
5. Basu J, Willard HF. Artificial and engineered chromosomes: non-integrating vectors for gene therapy. *Trends Mol Med* 2005; 11: 251–8.
6. Barzon L, *et al.* Versatility of gene therapy vectors through viruses. *Expert Opin Biol Ther* 2005; 5: 639–62.
7. Sinn PL, *et al.* Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors—design, biosafety, and production. *Gene Ther* 2005; 12: 1089–98.
8. Wierdl M, Potter PM. Update on gene therapy approaches for cancer. *Curr Hematol Rep* 2005; 4: 294–9.
9. Hart SL. Lipid carriers for gene therapy. *Curr Drug Deliv* 2005; 2: 423–8.
10. Kaplan JM. Adenovirus-based cancer gene therapy. *Curr Gene Ther* 2005; 5: 595–605.
11. Ohlfest JR, *et al.* Nonviral vectors for cancer gene therapy: prospects for integrating vectors and combination therapies. *Curr Gene Ther* 2005; 5: 629–41.
12. Dobson J. Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther* 2006; 13: 283–7.
13. Pelletier R, *et al.* RNA based gene therapy for dominantly inherited diseases. *Curr Gene Ther* 2006; 6: 131–46.
14. Park F, Gow KW. Gene therapy: future or flop. *Pediatr Clin North Am* 2006 Aug: 621–38.
15. Lavigne MD, Gorecki DC. Emerging vectors and targeting methods for nonviral gene therapy. *Expert Opin Emerg Drugs* 2006; 11: 541–57.
16. Chan S, Harris J. The ethics of gene therapy. *Curr Opin Mol Ther* 2006; 8: 377–83.
17. Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: are we there yet? *J Clin Invest* 2007; 117: 1456–65.
18. Kohn DB, Candotti F. Gene therapy fulfilling its promise. *N Engl J Med* 2009; 360: 518–21.

Gentian

Bitter Root; Enzianwurzel; Genciana; Genciana mayor; Gencijonų šaknys; Gentian Root; Gentiana; Gentianae Radix; Gentianarot; Gentiane; Gentiane, racine de; Genziana; Hořcový kořen; Katkeronjuuri; Korzeń goryczki; Raiz de Genciana; Tárnicsgyökér; Горький Корень.
ATC Herb — HA05AW5010 (Gentiana lutea: root); HA09WA5013 (Gentiana lutea: root).
UNII — S72O3284MS.

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

Jpn includes Japanese Gentian, from *G. scabra* and other species. *Chin.* also specifies *G. scabra* and other species.

Ph. Eur. 8: (Gentian Root; Gentian BP 2014). The dried, fragmented underground organs of *Gentiana lutea* yielding not less than 33% of water-soluble extractive. It has a characteristic odour. Protect from light.

Profile

Gentian is used as a bitter. An alcoholic infusion of gentian, bitter-orange peel, and lemon peel has been used as an ingredient in bitter mixtures.

Homoeopathy

Gentian has been used in homoeopathic medicines under the following names: Gentiana lutea; Gentiana lut; Gent. lut.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Underberg†.

Multi-ingredient Preparations. *Austral.*: Calmo†; Detox Program; Digest Aid; DiGest; Digestaid; Digestive Aid; Digestive Bitters; Extralife Sleep-Care†; Sinupret; Toxicol; *Austria*: Abdomilon N; Brady's-Magentropfen; China-Eisenwein†; Klosterfrau Melissengeist; Mariazeller; Montana; Pervivo; Sigman-Haustropfen; Sinupret; Solvopret†; *Braz.*: Camomila; Gotas Digestivas; Gotas Preciosas; *Canad.*: Gallexier†; Herbal Laxative plus Yogurt†; Herbal Laxative†; Para-Gard; Para-Gone; Stomach Ease; *Cz.*: Biotussil; Dr Theiss Schweden Krauter†; Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Original Schwedenbitter; Sinupret; *Fr.*: Diatisan†; Quintonine†; *Ger.*: Abdomilon N; Amara-Pascoe; Amara-Tropfen; Gallexier; Infi-tract V; Klosterfrau Melissengeist; Montana N; Schwedentrunk Elixier; Sedovent†; Sinupret; ventri-loges N†; *Hong Kong*: Sinupret; *Hung.*: Bano Svedkeseru; Bittner; Gallexier; Kalms; Klosterfrau Melisana; Montana; Sinupret; *Indon.*: Sinupret†; *Ital.*: Amaro Medicinale; Bulboshap†; Caramelle alle Erbe Digestive; *Malaysia*: Sinupret; *Mex.*: Bisolsinus; *Philipp.*: Sinupret; *Pol.*: Dyspepsin; Kalms; Melisana Klosterfrau; Pervivo; Sinupret; *Rus.*: Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sinupret (Синупрет); *S.Afr.*: Amara†; Enzian Anaemodoron Drops†; Helmontskruie†; Lewensessens; Versterkdruppels; Wonderkroonessens; *Singapore*: Sinupret; *Spain*: Depurativo Richelet†; *Swed.*: Galexir; Sinova; *Switz.*: Gastrosan; Gouttes Amara; Kemosan 26; Metabol; Padma-Lax; Padmed Laxan; Sinupret; Strath Gouttes pour l'estomac; Wala Elixir amer; *Thai.*: Pepsitase; Sinupret†; *UK*: Acidosis; Appetiser Mixture; Effico; Indigestion Mixture; Kalms; Quiet Tyme; Scullcap & Gentian Tablets; Sinueeze; Sinuherb; Stomach Mixture; *Ukr.*: Herbion Drops for the Stomach (Гербион Желудочные Капли)†; Sinupret (Синупрет); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; *Venez.*: Nov'Hepar B-12.

Homoeopathic Preparations. *Austria*: Aflubin; Lymphomyosot; Metavirulent; *Canad.*: Amaratopfen†; Vegetal Tonic; *Chile*: Bioactiv A; *Cz.*: Lymphomyosot; *Fr.*: Cereales Germees; Gentiana Complexe No 33†; Sativol†; Tonique Vegetal; *Ger.*: Gastrin-Do; K 1000; Lymphomyosot N; Lymphomyosot; Magen-Darmtropfen N; metavirulent; *Hung.*: Aflubin; Lymphomyosot; *Neth.*: Sativol†; *Rus.*: Aflubin (Афлубин); *S.Afr.*: Achillea Comp†; Lymphomyosot; *Ukr.*: Aflubin (Афлубин); Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pharmacopoeial Preparations
BP 2014: Acid Gentian Mixture; Alkaline Gentian Mixture; Compound Gentian Infusion; Concentrated Compound Gentian Infusion;
Ph. Eur.: Gentian Tincture.

Geraniol

Lemonol; Гераниол.
(*E*)-3,7-Dimethyl-2,6-octadien-1-ol.
$C_{10}H_{18}O=154.3$
CAS — 106-24-1.
UNII — L837108USY.

Profile

Geraniol is a constituent of several essential oils and is used in insect repellent preparations. It was formerly used as an anthelmintic. Geraniol is also used as a flavour and in perfumery. Contact dermatitis has been reported.

References.

1. Yamamoto A, *et al.* Contact urticaria from geraniol. *Contact Dermatitis* 2002; 46: 52.
2. Murphy LA, White IR. Contact dermatitis from geraniol in washing-up liquid. *Contact Dermatitis* 2003; 49: 52.
3. Tamagawa-Mineoka R, *et al.* Allergic contact cheilitis due to geraniol in food. *Contact Dermatitis* 2007; 56: 242–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Cholestin.

Multi-ingredient Preparations. *Canad.*: Natrapel Plus.

Geranium Oil

Aetheroleum Pelargonii; Geranii Etheroleum; Geranio, aceite esencial de; Geraniová silice; Oleum Geranii; Pelargonium Oil; Rose Geranium Oil; Гераниевое Масло.
UNII — 5Q1I94P4WG.

Profile

Geranium oil is a volatile oil obtained by distillation from the aerial parts of various species and hybrid forms of *Pelargonium* (Geraniaceae). It contains geraniol (above). It is used to perfume various preparations and has been included in insect repellent preparations. It is also used in aromatherapy.

Postherpetic neuralgia. A study[1] involving 30 patients has indicated that topically applied geranium oil is of benefit in the management of the pain of postherpetic neuralgia. Pain relief was obtained within a few minutes but further study is required to determine the duration of effect beyond 1 hour. Adverse effects were considered to be minor and included burning in the eye, rash, and light-headedness.

1. Greenway FL, *et al.* Temporary relief of postherpetic neuralgia pain with topical geranium oil. *Am J Med* 2003; 115: 586–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Entom Nature.

Multi-ingredient Preparations. *Austral.*: Advanced Menopause Care; *Fr.*: Buvanol; *India*: Nasoclear Aloegel; *Ital.*: Dentosan Azione Intensiva; Dentosan Mese; Mistick Verde; *NZ*: Mr Nits; *Singapore*: Teenstick; *UK*: Medicated Extract of Rosemary; Nostroline; Repelselect; Teenstick.

Homoeopathic Preparations. *UK*: Medicinal Gargle.

Germanium

Germanio; Германий.
Ge=72.630
CAS — 7440-56-4.
UNII — 00072J7XWS (germanium); TY8J0G7KOD (germanium ion).

Profile

Germanium compounds have been used in dietary supplements promoted for conditions including cancer, chronic fatigue syndrome, and immunodeficiency disorders. However, germanium compounds can produce severe renal damage and their use should be discouraged.

Germanium has also been used in dental alloys and has various industrial uses.

Effects on the kidneys. In the UK the DoH has recommended that germanium should not be taken as a dietary supplement because of a significant incidence of renal toxicity. There have been several reports of severe renal damage, including fatalities, resulting from germanium ingestion.

References.

1. Okada K, *et al.* Renal failure caused by long-term use of a germanium preparation as an elixir. *Clin Nephrol* 1989; 31: 219–24.
2. van der Spoel JI, *et al.* Dangers of dietary germanium supplements. *Lancet* 1990; 336: 117. Correction. *ibid.* 1991; 337: 864.
3. Schauss AG. Nephrotoxicity in humans by the ultratrace element germanium. *Ren Fail* 1991; 13: 1–4.
4. Hess B, *et al.* Tubulointerstitial nephropathy persisting 20 months after discontinuation of chronic intake of germanium lactate citrate. *Am J Kidney Dis* 1993; 21: 548–52.
5. Tao SH, Bolger PM. Hazard assessment of germanium supplements. *Regul Toxicol Pharmacol* 1997; 25: 211–19.
6. Swennen B, *et al.* Epidemiological survey of workers exposed to inorganic germanium compounds. *Occup Environ Med* 2000; 57: 242–8

Gevokizumab (USAN, rINN)

Gevokizumab; Gevokizumabum; XOMA-052; Гевокизумаб.
Immunoglobulin G2, anti-(human interleukin 1β) (human-*Mus musculus* XOMA 052 heavy chain), disulfide with human-*Mus musculus* XOMA 052 κ-chain, dimer.
CAS — 1129435-60-4.
UNII — OX3JU54GYQ.

Profile

Gevokizumab is a humanised anti-interleukin-1β monoclonal antibody that is under investigation for the treatment of non-infectious uveitis such as Behçet's disease.

References.

1. Owyang AM, *et al.* XOMA 052, a potent, high-affinity monoclonal antibody for the treatment of IL-1 β -mediated diseases. *MAbs* 2011; 3: 49–60.
2. Gül A, *et al.* Interleukin-1 β -regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behcet's disease: an open-label pilot study. *Ann Rheum Dis* 2012; 71: 563–6.

Ginkgo Biloba

Árbol de los cuarenta escudos; EGB-761; Fossil Tree; GBE-761; Ginkgo, feuille de (ginkgo leaf); Ginkgo folium (ginkgo leaf); Ginkgoblad (ginkgo leaf); Ginkmedžių lapai (ginkgo leaf); Jinanový list (ginkgo leaf); Kew Tree; Maidenhair Tree; Neidonhiuspuunlehti (ginkgo leaf); *Salisburia adiantifolia*; Páfrányfenyőlevél (ginkgo leaf); Гинкго Билоба.
ATC — N06DX02.
ATC Vet — QN06DX02.
ATC Herb — HN07CA5001 (Ginkgo biloba: leaf); HC04AW5001 (Ginkgo biloba: leaf); HN06DX5001 (Ginkgo biloba: leaf).
UNII — 660486U6OI (Ginkgo biloba); T9FUJ2C58T (Ginkgo biloba leaf); Y5967KO1JH (Ginkgo biloba leaf water); 1XUK686051 (Ginkgo biloba root); 8CQ734K3W7 (Ginkgo biloba seed).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*. *Eur.* (see p. vii) also includes Ginkgo Dry Extract, Refined and Quantified. *US* includes a powdered extract.

Ph. Eur. 8: (Ginkgo Leaf). The whole or fragmented dried leaf of *Ginkgo biloba* containing not less than 0.5% of flavonoids, calculated as flavone glycosides with reference to the dried drug. The leaf is greyish or yellowish-green or yellowish-brown.

USP 36: (Ginkgo). The dried leaf of *Ginkgo biloba* (Ginkgoaceae) containing not less than 0.5% of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7, and not less than 0.1% of terpene lactones, both on the dried basis. The leaf is khaki green to greenish-brown. Protect from light and moisture.

Uses and Administration

An extract from the leaves of *Ginkgo biloba* has been used in cerebrovascular and peripheral vascular disorders. It is also being investigated in Alzheimer's disease, multi-infarct dementia, and in tinnitus. *Ginkgo biloba* is a source of ginkgolides (below).

Homoeopathy

Ginkgo biloba has been used in homoeopathic medicines under the following names: Ginkgo.

General references.

1. WHO. Folium Ginkgo. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/18.html (accessed 04/02/10)

Cerebrovascular disorders. A systematic review[1] of 10 randomised or quasi-randomised studies concluded that the routine use of ginkgo biloba extracts to promote recovery after ischaemic stroke was not supported by any convincing evidence, and that larger better quality studies were required.

1. Zeng X, *et al.* Ginkgo biloba for acute ischaemic stroke. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/05/06).

Dementia. Ginkgo biloba extracts have been tried in the treatment of dementia including Alzheimer's disease (p. 388.1). Meta-analyses[1,2] have found the extracts to be more effective than placebo in some cases. However, a later systematic review[3] concluded that there is inconsistent and unreliable evidence that ginkgo biloba has any benefit for people with dementia or cognitive impairment. Furthermore, these authors felt that conventional studies for its use in the treatment of acquired cognitive impairment were unlikely to prove useful, although studies in patients with neuropsychiatric symptoms might be warranted. A study[4] assessing whether ginkgo biloba can prevent cognitive decline in very elderly people with normal memory function found positive effects only after adjustment for noncompliance. However, more cases of stroke or transient ischaemic attacks were noted in those given ginkgo biloba although further study is required to confirm any link. Another study[5] investigating the effect of ginkgo biloba in reducing the incidence of dementia in people over 75 years of age with normal cognition or mild cognitive impairment found that it was ineffective.

1. Oken BS, *et al.* The efficacy of ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 1998; 55: 1409–15.
2. Ernst E, Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 1999; 17: 301–8.
3. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 08/12/09).
4. Dodge HH, *et al.* A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 2008; 70: 1809–17.
5. DeKosky ST, *et al.* Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* 2008; 300: 2253–62. Correction. *ibid.*: 2730.

Peripheral vascular disorders. Ginkgo biloba extracts have been tried in the treatment of peripheral vascular disorders (p. 1272.3). A meta-analysis[1] found the extracts to be more effective than placebo in the symptomatic treatment of intermittent claudication, although the authors considered the size of the effect to be modest and of uncertain clinical relevance. A later systematic review[2] found no evidence of a clinically significant benefit for patients with peripheral arterial disease.

1. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000; 108: 276–81.
2. Nicolai SPA, *et al.* Ginkgo biloba for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 08/12/09).

Tinnitus. Ginkgo biloba extracts have been tried in the treatment of tinnitus (p. 1990.1). A systematic review[1] of 5 randomised controlled studies cautiously concluded that these results were favourable, although a later systematic review[2] failed to show benefit.

1. Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clin Otolaryngol* 1999; 24: 164–7.
2. Hilton MP, Stuart EL. Ginkgo biloba for tinnitus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 08/12/09).

Adverse Effects and Precautions

Adverse effects of ginkgo biloba include headaches, dizziness, palpitations, gastrointestinal disturbances, bleeding disorders, and skin hypersensitivity reactions.

Poisoning. Convulsions are a known effect of consuming large amounts of ginkgo seeds.[1,2] The effect is considered to be due to ginkgotoxin (4-metoxypyridoxine, 4′-*O*-methylpyridoxine), which is present in the raw seeds in amounts of up to 85 micrograms per seed.[3] It is also present in smaller amounts in the leaves, and has been detected in proprietary products in variable quantities that would correspond to a daily dose of up to about 60 micrograms. There have been a few reports of convulsions associated with ginkgo biloba products, and it has been suggested that they should be used with caution in patients with epilepsy.[3] Giving suitable quantities of a vitamin-B_6 source might be of benefit in preventing ginkgotoxin-induced convulsions.[2]

1. Miwa H, *et al.* Generalized convulsions after consuming a large amount of gingko nuts. *Epilepsia* 2001; 42: 280–1.
2. Kajiyama Y, *et al.* Ginkgo seed poisoning. *Pediatrics* 2002; 109: 325–7.
3. Leistner E, Drewke C. *Ginkgo biloba* and ginkgotoxin. *J Nat Prod* 2010; 73: 86–92.

Pregnancy and breast feeding. There is weak evidence from *animal* and *in-vitro* studies that ginkgo biloba has antiplatelet activity and therefore its use during labour could possibly prolong bleeding time.[1] There are no data on its safety during breast feeding.

1. Dugoua J-J, *et al.* Safety and efficacy of ginkgo (Ginkgo biloba) during pregnancy and lactation. *Can J Clin Pharmacol* 2006; 13: e277–e284.

Interactions

It has been suggested that ginkgo biloba should be used with caution in patients receiving anticoagulants or drugs that affect platelet aggregation. For reference to a possible interaction with *warfarin*, see p. 1534.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Clarvix; Kalter; Tanakan; *Austral.*: Ginkgoforte; PM Remem; *Austria*: Cerebokan; Cerefemin; Gingolt†; Tebofortan; Tebonin; *Belg.*: Tanakan; Tavonin; *Braz.*: Binko; Bioflavin†; Clibium; Dinaton; Equitam; Gibilon; Ginbiloba; Gincobem; Gincolin; Ginkoba; Ginkogreen; Ginkolab; Ginkomed; Ginkoplus†; Ginkotab; Gyncobem; Kirsan; Oxian†; Tanakan; Tebiloba; Tebonin; Tekasan; *Chile*: Ginkomax; Kladon; Memokit†; Nokatar; Rokan; *China*: Ginaton (金纳多); Tanakan (达纳康); Yin Ke Luo (银可络); *Cz.*: Gingio; Tanakan; Tebokan; *Fr.*: Ginkogink; Tanakan; Tramisal; Vitalogink; *Ger.*: Duogink†; Floragink; Gingiloba†; Gingium†; Gingobeta†; Gingopret; Ginkobil; Ginkodilat†; Ginkopur; Kaveri; Rokan; Tebonin; *Gr.*: Tanacain; Tebokan; *Hong Kong*: Ebamin†; Ginkolin†; Tanakan; *Hung.*: Bilobil; Gingium; Salus Floragink; Tanakan†; Tebofortan; *India*: Avon; Bilovas; Cerestar; Geritisin; Gibil; Gincer; Ginkoba; Ginkocer; Ginkoriv; Ginvas; *Indon.*: Brenax; Gingkan†; Ginkgoforce; Ginkona; Lanaginkola; Tebokan; *Ital.*: Ginkoba; *Malaysia*: Giloba; Gincare; Lanaginkola; Tanakan; Tebonin; *Mex.*: Nemoril; Tebonin; Vasodil; *Neth.*: Tavonin; *Norw.*: Bio-Biloba; Memoplant†; Seredrin†; *Philipp.*: Ginkocer†; Tebokan; Tebonin; *Pol.*: Bilobil; Flavobil; Geriacaps; Ginkgofol; Ginkgomax†; Ginkofar; Herbabiloba†; Memoplant; Tanakan; *Port.*: Abolibe; Biloban; Gincoben; Vasactife; *Rus.*: Bilobil (Билобил); Gingium (Гинкгум); Ginkgoum (Гинкоум); Ginos (Гинос); Memoplant (Мемоплант); Tanakan (Танакан); *Singapore*: Giloba; Gincare; Ginkapran; Ginkosen; Gitako; Neuroxin†; Tanakan; Tebonin; *Spain*: Fitokey Ginkgo†; Ginkgold; Ginkokan; Incebral; Normoginkgo; Tanakene; *Swed.*: Bio-Biloba; *Switz.*: Demonatur Ginkgo†; Geriaforce; Gingosol†; Sanapens†; Symfona; Symfonel; Talent†; Tanakene†; Tebofortin; Tebokan; *Thai.*: Tanakan; Tebonin; *Turk.*: Gineksin F; Gingobil; Tanakan; *UK*: Gingkoforce; Ginkovital; *Ukr.*: Bilobil (Билобил); Giloba (Гилоба); Memoplant (Мемоплант); Tanakan (Танакан); Vobilon (Вобилон); *USA*: BioGinkgo; *Venez.*: Kladon; Neukob; Tanakan; Tebokan; Varginko.

Multi-ingredient Preparations. *Arg.*: ADX; Aulis; Biovital Pro Q10; Cellasene Gold; Cellasene†; Centella Queen Complex; Centellase de Centella Queen; Ciprovit Energizante; CVP Cellulite; Desgras Piel Naranja; Fioton; Flebitol; GB 100; Gentianella; Ginkgo Biloba Forte; Ginkgo Biloba Memo Diates†; Ginkgo Forte; Herbaccion Celfin; Herbaccion Memory; Ivix; Lopecian; Neurotonl†; SCV 300; Snell Patch; Snell Progress; Varicofem; Venofuli; Vita 1000 Plus; VNS 45; *Austral.*: Aesculus & Ruscus Compound; Bacopa & Ginkgo Compound; Bilberry Plus Eye Health†; Clements Tonic; Extralife Extra-Brite†; Extralife Eye-Care†; Extralife Leg-Care†; Eye Health Herbal Plus Formula 4†; For Peripheral Circulation Herbal Plus Formula 5†; Gincosan; Ginkgo Brahmi; HerbaVital; Horsechestnut Complex; Mens Dual-Action Multi; Mens Performance Multi; Mindac; Multi + Ginkgo for 55+†; PM LifeBrain; PM LifePro Max for Men; Prosense for Men†; PulmaCo; VIG; Vision-Eze†; Zellulean with Escin†; *Braz.*: Minesol; *Canad.*: Libeeda for Women; *Chile*: Celltech; Gincosan; Mentania; Perfect Body; Podexine Pie Diabetico; Sebium AKN†; *China*: Ginkor Fort (静可福); *Cz.*: Bilobil Duo; Gincosan; Ginkor Fort; *Fr.*: Diozinac KS; Diozinac; Ginkor Fort; Ginkort†; Memoptic; OM3memory†; ProstaSecurA; Sebium AKN; *Ger.*: Trium; *Hong Kong*: Doctor's Choice Multivitamins and Minerals for Eyes; Flavo-C†; Ginkgo-PS†; Ginkor Fort; *Hung.*: Gincosan; Ginkor Fort†; *India*: Bil-B; Bio-Loba; Enlarge; Full-24; GGG-24; Ginkoriv Plus; Goldcare; Jini; Multivite Gold; Multivite Woman; *Indon.*: Bilotec; Cerebrovit Senior; Cereton; Ginokan†; Hemaviton Brain Nutrient†; Proseval; Proview; *Ital.*: Angioton; Angiovein; Artedin; Blunorm; Criotonal; Eccarvit Plus; Energeia; Flavogin Plus; Fon Wan Memory; Forticrin; Fosfaserin; Ginkoftal; Ginkoret; Lik-Gel†; Macvit; Memovigor; Mentvis; Neuralta Migren; Otobrain; Pik Gel; Pulsalux; Vasobrain Plus; Vasobrain; Vasopt; Vasotonal; Venalta; Vertiginkgo; Vitalmix Fos; *Malaysia*: Circarol; Gincosan; Ginkor Fort; *Mex.*: Biometrix†; Maxibiloba; *Mon.*: Phytospray; *Philipp.*: Circulan; Nutricap; Nutrotal; *Pol.*: Bioginko; Cardiobonisol; Ginkgocard†; Intelektan†; Passibil; Venoforton; *Rus.*: Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); *Singapore*: Ginkgo-PS†; NutraMX; Robovites Multivitamins; Vitaton Gold; *Switz.*: Allium Plus†; Arterosan Plus†; Gincosan; *Thai.*: Gilomax; Ginkor Fort; *UK*: Goldcare; Neuro Nutrients; ProBrain; *Ukr.*: Ginkor Fort (Гинкор Форт); Ginkor Gel (Гинкор Гель); Goldcare (Голдкеа); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Intellan (Интеллан); Memory Booster (Мемори Бустер); Neokardil (Неокардил); Osteoartisi Max (Остеоартизи Макс); Theravit Antistress (Теравит Антистресс); Vitrum Memory (Витрум Мемори); *USA*: Aphrofem; Blood Sugar Balance; Cavigen; Diabetiks; Dorofen; Gentaplex; PowerMate; Sunnie; *Venez.*: Sebium AKN; Sengobil.

Homoeopathic Preparations. *Austria*: Cefavora; Memoria; *Canad.*: Formula CI 207†; Formula Homeo QR 209†; Ginkgo-Comp†; *Ger.*: Cefavora G†; Cefavora†; Geriaforce†; Ginkgo biloba comp; Ginkgobakehl; Ginkgorell; metaginkgo†; *Rus.*: Memoria (Мемория); *Switz.*: Ginkgobakehl; metaginkgo; *Ukr.*: Cefavora (Цефавора); Memoria (Мемория).

Pharmacopoeial Preparations

USP 36: Ginkgo Capsules; Ginkgo Tablets.

Ginkgolides

Ginkgolidos; Гинкголиды.

CAS — 15291-75-5 (ginkgolide A); 15291-77-7 (ginkgolide B); 15291-76-6 (ginkgolide C).

Profile

Ginkgolides are terpenoid molecules isolated from *Ginkgo biloba* (p. 2512.3), with platelet-activating factor (PAF) antagonist properties. They have been investigated as BN-52063, a mixture of ginkgolides A (BN-52020), B (BN-52021), and C (BN-52022), for asthma and other inflammatory and allergic disorders, and also in immune disorders such as endotoxic shock and graft rejection; ginkgolide B, which has the most potent PAF antagonist properties, has been tried alone in similar conditions.

Other ginkgolides, including ginkgolide M (BN-52023) and ginkgolide J (BN-52024), have also been identified.

References.

1. Braquet P. The ginkgolides: potent platelet-activating factor antagonists isolated from Ginkgo biloba L: chemistry, pharmacology and clinical applications. *Drugs Of The Future* 1987; 12: 643–99.
2. Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet* 1992; 340: 1136–9.
3. Houghton P. Ginkgo. *Pharm J* 1994; 253: 122–3.
4. Brochet B, *et al.* The Ginkgolide Study Group in Multiple Sclerosis. Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; 58: 360–2.
5. Maclennan KM, *et al.* The CNS effects of Ginkgo biloba extracts and ginkgolide B. *Prog Neurobiol* 2002; 67: 235–57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Bilokan; Seremaks; Tebokan.

Multi-ingredient Preparations. *Ital.*: Perfluxi Cremagel.

Ginseng

Ginseng radix; Ginsengwurzel; Ginzenggyökér; Jintsam; Ninjin; Panax; Pannag; Renshen; Schinsent; Všehojový kořen; Ženšenių šaknys; Корень Жизни; Женьшень.

ATC Herb — HN06WA5002 (Panax ginseng: root).

UNII — CUQ3A77YXI (Panax ginseng root).

Description. Ginseng is the dried root of *Panax ginseng* (*P. schinseng*) (Araliaceae). Other varieties of ginseng include *Panax quinquefolius* (American Ginseng) and *P. pseudoginseng*. The root commonly known as Siberian or Russian ginseng belongs to the same family, Araliaceae, but is an entirely different plant, *Eleutherococcus senticosus* (see Siberian Ginseng, p. 2614.3). Brazilian ginseng is reported to be derived from another unrelated plant, *Pfaffia paniculata*. The name Indian Ginseng is used for the Ayurvedic medicine, Ashwagandha (see p. 2450.2).

Ginseng contains complex mixtures of saponins termed ginsenosides or panaxosides. At least 13 saponins have been isolated from extracts of *P. ginseng* roots.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*. Also in *US* (as Asian Ginseng and American Ginseng). *US* includes additionally powdered forms of these two varieties of ginseng. *Eur.* also includes the dry extract.

Jpn also includes Red Ginseng, the dried root of *P. ginseng* which has been steamed.

Chin. and *Jpn* also include the rhizome of *Panax japonicus*. *Eur.* (see p. vii) also includes Notoginseng Root from *P. notoginseng*. *Chin.* also includes Radix Notoginseng from *P. notoginseng*, and Rhizoma Panacis Majoris from *P. japonicus* var. *major* and *P. japonicus* var. *bipinnatifidus*.

Ph. Eur. 8: (Ginseng). The whole or cut dried root of *Panax ginseng*. It contains not less than 0.4% of combined

ginsenosides, Rg1 ($C_{42}H_{72}O_{14}.2H_2O$ = 837.1) and Rb1 ($C_{54}H_{92}O_{23}.3H_2O$ = 1163.4), calculated with reference to the dried drug. Protect from light.

USP 36: (Asian Ginseng). The dried roots of *Panax ginseng* (Araliaceae). It contains not less than 0.2% of ginsenoside Rg_1 and not less than 0.1% of ginsenoside Rb_1, both calculated on the dried basis. Store in a dry place at a temperature of 8 degrees to 15 degrees.

USP 36: (American Ginseng). The dried roots of *Panax quinquefolius* (Araliaceae). It contains not less than 4.0% of total ginsenosides, calculated on the dried basis. Store in airtight containers. Protect from light and heat.

Uses and Administration

Ginseng is reported to enhance the natural resistance and recuperative power of the body and to reduce fatigue. It is available commercially as roots, powdered roots, tablets, capsules, teas, oils, or extracts.

General references.

1. WHO. Radix Ginseng. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/19.html (accessed 04/02/10)

Adverse Effects

A 2-year study[1] of ginseng in 133 subjects who had used commercial preparations including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum, and candies reported that the majority of preparations were taken orally, but a few subjects had experimented with intranasal or parenteral routes, and topical preparations had also been used. The stimulant effects of ginseng were confirmed but there was also a high incidence of adverse effects including 47 cases of morning diarrhoea, 33 of skin eruptions, 26 of sleeplessness, 25 of nervousness, 22 of hypertension, 18 of euphoria, and 14 of oedema. The 'ginseng abuse syndrome' defined as hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhoea was experienced by 14 subjects who took ginseng root material orally in an average daily dose of 3 g. Abrupt withdrawal precipitated hypotension, weakness, and tremor in 1 user. About 50% of the subjects had stopped the use of ginseng within the 2 years. Oestrogenic effects have also been reported from the use of ginseng,[2-4] and a case of Stevens-Johnson syndrome has also occurred.[5]

A systematic review[6] of some of these and other studies and case reports concluded that single-ingredient preparations of ginseng were well tolerated when data from clinical studies were examined. Adverse effects were generally mild and reversible, the most common being headache, sleep disturbances, and gastrointestinal disorders. It was more difficult to determine causality from the evidence given in isolated case reports; likewise, interpretation of data involving combination products was difficult.

Ginseng was also reported[7] to be well tolerated in a paediatric study in which 46 children aged between 3 and 12 years were randomly assigned to receive ginseng or placebo as a 3-day treatment course for upper respiratory-tract infections.

1. Siegel RK. Ginseng abuse syndrome: problems with the panacea. *JAMA* 1979; 241: 1614–15.
2. Palmer BV, *et al.* Gin Seng and mastalgia. *BMJ* 1978; 1: 1284.
3. Punnonen R, Lukola A. Oestrogen-like effect of ginseng. *BMJ* 1980; 281: 1110.
4. Greenspan EM. Ginseng and vaginal bleeding. *JAMA* 1983; 249: 2018.
5. Dega H, *et al.* Ginseng as a cause for Stevens-Johnson syndrome? *Lancet* 1996; 347: 1344.
6. Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Safety* 2002; 25: 323–44.
7. Vohra S, *et al.* Safety and tolerability of North American ginseng extract in the treatment of pediatric upper respiratory tract infection: a phase II randomized, controlled trial of 2 dosing schedules. *Pediatrics* 2008; 122: 428. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/2/e402.pdf (accessed 16/08/10)

Interactions

For reports of interactions between *phenelzine* and ginseng, see p. 446.2. For details of an interaction between *warfarin* and ginseng, see p. 1534.2. For a suggestion that ginseng may interfere with *digoxin* assays, see p. 1355.3. For a suggestion of a potential interaction between ginseng and *tamoxifen*, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ginsana; Herbaccion Bioenergizante; *Austria*: Ginsana; *Belg.*: Ginsana†; *Braz.*: Bioplus; Enerseng†; Fortilan; Fotilan; Ginsana; Ginsex; Revigonal; *Canad.*: Cold-FX; Nurite; *Cz.*: Ginsana†; *Fr.*: Gerimax Tonique†; Tonigin†; *Ger.*: Ardey-aktiv; Ginsana; IL HWA; Orgaplasma; *Irl.*: Ginsana; *Ital.*: Fon Wan Ginsenergy; Ginsana; *Jpn*: Koujin; *Malaysia*: Ginsana†; *Mex.*: Rutying; Sanjin Royal Jelly; *Norw.*: Ginsana; *Pol.*: Ginsana†; Ginsenol; Panaxan†; *Port.*: Ginsana; *Rus.*: Gerimax Ginseng (Геримакс Женьшень); Ginsana (Гинсана); Herbion Zen Sen (Гербион Женьшень); *Singapore*: Ginsana†; *Spain*: Bio-Star†; Energin; Redseng; *Swed.*: Ginsana; *Switz.*: Ginsana; Ginsor; IL HWA; KintaVital; *Thai.*: Ginsana†; Ginsroy; Pharmagin; *UK*: Korseng; Red Kooga; *Ukr.*: Gerimax Ginseng (Геримакс Женьшень).

Multi-ingredient Preparations. *Arg.*: ADX; CTabs-Total Vit; Dynamisan; Energizante Vital con ginseng; Energy Plus; Fospartan Ginseng; Galenic Restaurador Capilar; Gingeron; Ginseng Bioplus Diates†; Herbaccion Ginseng y Magnesio; Holomagnesio Vital; Inmunofit; KH3†; Level Up; Magnesio 102 Plus; Marathon; Masvitalin Ginseng; Megamax; Merebral; Neuroton†; Optimina Fem; Optimina Plus; Pharmafort; Pharmaton Complex; Pharmaton; Plenovit; Polper Ginseng†; Stimulnerv; Tanvimil Ginseng; Total Magnesiano con Ginseng; Total Magnesiano con Vitaminas y Minerales; Total Magnesiano E; Total Magnesiano Sport; Vifortol; Vitagenol Plus; *Austral.*: Aloe Vera Plus; Clements Tonic; Daily Plus Max†; Everyday Stress Formula; Extralife Extra-Brite†; Gincosan; Ginsynergy plus Rhodiola; Hairy Lemon; HerbaVital; Irontona†; Memory and Vitality Formula; Nervatona Focus; PM LifePro Max for Women; Prosense for Women†; ViG; Vitatona†; Wild Yam Complex; Withania Complex; *Austria*: Geriatric Pharmaton; ProAktiv; *Belg.*: Ostrin Q10; *Braz.*: Geriaton; Geriavite; Gerilon; Gerin; Gerovital; Natus Gerin; Pharmaton; Poliseng; Vita Senior; Vitergan Master; *Canad.*: Libeeda for Men; *Chile*: Bedovit Pharmaton; Biocord-E; Biocord; Capilet Locion Capilar; Diltotal; Dynamisan; Enerday; Fortavil; Gincosan; Infor; Marathon; Mentania; Nectaday†; Pantiban†; Pharmaton; Salubion Ginseng; Supradyn Ginseng; Tolgin†; Tonopron Ginseng; Ultrac E; Ultrac Q10; Ultrac; Vitamix; *China*: Supradyn (维多宝); *Cz.*: Bilobil Duo; Geriavit; Gincosan; Pharmaton Activit; *Fr.*: Alvityl Tonus; Aromavital†; Bion 3 Seniors; Bryssidine; Cicatendon; Dynabiane; Elusanes Starphyt†; Fibromyalgine Fort; Gerimax adultes†; Gestarelle S; Magneginseng†; Normalite 1000; Pharmaton†; Tigre de Chine; Tonactil†; *Ger.*: Pharmaton; *Gr.*: Pharmaton Geriatric; *Hong Kong*: Pharmaton; Sanjukei Panax Ginseng; Wellman†; Wellman; *Hung.*: Flu-Vit; Gerimax; Gincosan; Pharmaton Vital; Sam-Ginseng Royal; *India*: Anvital; Ashwita; Beminal; Biostar; Biotone-TD; Biovital; Cad-Vital; Canzeal; Curevital; Cuvital; Dayvital; Elvital-SG; Enlarge; Everfit; Full-24; GB-Lex; Gen-One; Genmac; Gevital; GGG-24; Ginkoriv Plus; Ginsiplex; Gintox; Ginvit; Glofit Plus; Goldcare; GS Forte; GVM; Intavital; Keep-Fit; Lupivital; Lycopol; Lyrich-G; Malvit; Mezica; Minero; Minvital; Multiging; Multiphar; Multivite Gold; Nu-Seng; Omnigen Forte; Orovital-G; Trinergic; Vitacip; *Indon.*: Armovit; Berocca Performance; Cerebrovit Active; Ginokan†; Hemaviton Action; Hemaviton Brain Nutrient†; Hemaviton Energy Drink; Hemaviton Jreng; Hemaviton Stamina Plus; Instink†; Maxirex; Menolia†; Neo Hormoviton Greng; Neo Hormoviton; Neo Hormoviton; Oramin-G; Penfri; Pharmaton Formula; Pharmaton Vit; Procur Plus; Proseval; Provital Plus; Provital; Ratax; Sirec; Stobled; Tripid; Tristan†; *Irl.*: Pharmaton; Seven Seas Active Sport†; *Israel*: Gerimax NF†; Pharmaton; Polyvit 30 Plus; *Ital.*: Alvear con Ginseng; Apergan; Bioestril Ginseng; Bioton; Enercomplex; Energeia; Euroton; Forticrin; Fosfarsile Forte†; Fosfarsile Forte; Fosfaserin; Gegorvit; Ginsana Ton; Multi Up; Neoplus; Ocustress; Ottovis; Pollingel Ginseng; Taingel; The Ginseng King†; Vitalmix Complex; Vitalmix Fast; *Jpn*: Bakumondoto; Bukuryoin; Bukuryoingohangekobokuto; Byakkokaninjinto; Chikujountanto; Chotosan; Daibofuto; Daikenchuto; Eki Cabe A†; Eki Cabe S; Goshuyuto; Hangebyakujutsutemmato; Hangeshashinto; Hochuekkito; Jinsoin; Juzentaihoto; Kamikihito; Keihito; Keishininjinto; Kihito; Mokuboito; Ninjin'yoeito; Ninjinto; Nyoshinsan; Orento; Q & P Gold; Rikkunshito; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishito; Saireito; Seishinrenshiin; Seishoekkito; Shakanzoto; Shikunshito; Shosaikoto; Shosaikotokakikyosekko; Tokito; Unkeito; *Malaysia*: 30 Plus†; Adult Citrex Multivitamin + Ginseng + Omega 3; Appeton; Enervon with Ginseng & Vitamin E; Gincosan; Ginsomin; Imuvit; NeuroAid; Pharmaton with Selenium; Pharmaton†; Proviton; Revital; Shine Growell; Shine Maxtra; *Mex.*: Biometrix†; Dynamisan; Pharmaton Complex; Pharmaton; Vitalaif; Wilvit; *Philipp.*: Arcostrong†; BSI Medicated Spray; Energel; Ginsomin; Havitall; Homtamin-G Plus; Immuvit; K-A Plus; Korgivit-E†; Memovit-E†; Nutricap; Nutrotal; Pharmaton; Polynerv-E with lecithin; Rejuvenex; Restor-P; Revicon Max; Rogin-E; SG-Glutergen; Supranutrol; Ultima; Vita SL; Vitaginseng; *Pol.*: Bioginko; Doppelherz Vital Kapseln†; Geriatrix; Geriavit†; Geronpol†; Ginjal; Intelektan†; Witagin; *Rus.*: Doppelherz Ginseng Aktiv (Доппельгерц Женьшень Актив); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Geriavit (Гериавит)†; Gerimax (Геримакс); Raylis (Райлис); Revital Ginseng Plus (Ревайтл Гинсенг Плюс)†; Theravit Tonic (Теравит Тоник); Vitamax (Витамакс)†; Wellman (Велмен); *S.Afr.*: Activex 40 Plus†; Gericomplex†; Pharmaton†; *Singapore*: Enervon with Ginseng & Vitamin E; Gin-Vita; Gingviton; Ginsomin; Immuvital; Neovita; Neovita; NutraMX; Pharmaton with Selenium; Pharmaton†; Provital; Vitaton Gold; Vitaton; *Spain*: Cinfavit Complex; Forcemil; Pharmaton Complex†; Redseng Polivit†; Ton Was; Vitestable; *Swed.*: Gericomplex; *Switz.*: Biorganic Geri; Biovital Ginseng; Burgerstein Top-Vital; Enuton†; Gincosan; Imuvit†; Imuvital†; Pharmaton Vital Geriavit; Pharmatovit Ginseng; ProActive; Supradyn Vital 50+; Tai Ginseng†; Tonique D liquide†; *Thai.*: Geriatric Pharmaton; Imugins; Imuvit; Multilim RG; Pharmaton Fizzi; Pharmaton; Revitan; *Turk.*: Pharmaton; *UAE*: Ginsavit; *UK*: Multiron; Neovita; Pharmaton; Red Kooga Co-Q-10 and Ginseng; Regina Royal Concorde; *Ukr.*: Alfagin (Алфагин); Energin (Энергин); Ginsomin (Гинсомин); Huato Pills (Болюсы Хуато); Mammoleptin (Маммолептин); Rotavit Royal (Ротавит Ройял); Theravit Antistress (Теравит Антистресс); Theravit Tonic (Теравит Тоник)†; Vitrum Energy (Витрум Энерджи); Wellman (Велмен); Yohimbex-Garmonia (Йохимбекс-Гармония); *USA*: Clinical Nutrients 50-Plus Men; Dexatrim Max Daytime Appetite Control; Immunicare; *Venez.*: Energyvit; Hivit; Kinerton; Multivi Natura; Pharmorat; Sengobil; Vigoran.

Homoeopathic Preparations. *Austral.*: Nervatona Focus; *Austria*: Erbiode-Starkungstropfen; Memoria; Orgafem; Selenium Me Complex; *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic Formula FA 224†; *Cz.*: Vita C-R15 forte†; *Fr.*: Selenium Complexe No 99; *Ger.*: K 1000; Manuia; Neuri-cyl N Ho-Len-Complex; Neuro-Ginsan N; Schworocor A; Tondinel; *Rus.*: Damiana-Plus (Даммана-Плюс); Memoria (Меморя); *Ukr.*: Memoria (Меморя).

Pharmacopoeial Preparations

USNF 31: American Ginseng Capsules;

USP 36: American Ginseng Tablets; Asian Ginseng Tablets.

Glatiramer Acetate *(BAN, USAN)*

COP-1; Copolímero I; Copolymer 1; Glatirameeriasetaatti; Glatiramer, acetato de; Glatiramer Asetat; Glatirameracetat; Glatirameri Acetas; Глатирамер Ацетат.

L-Glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate.

CAS — 28704-27-0 (glatiramer); 147245-92-9 (glatiramer acetate).

ATC — L03AX13.

ATC Vet — QL03AX13.

UNII — 5M691HL4BO.

Uses and Administration

Glatiramer acetate, a random polymer of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, is a polypeptide that has some structural resemblance to myelin basic protein. It is used to reduce the frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis (p. 996.3), including patients with a well defined first clinical episode and deemed to be at high risk of developing clinically definite multiple sclerosis. Although its precise mechanism of action in multiple sclerosis is unknown, it is thought to modify immune processes involved in the pathogenesis. Glatiramer acetate is given by subcutaneous injection in a dose of 20 mg once daily. It should not be given by the intravenous or intramuscular route. An oral formulation has been investigated with disappointing results.

Multiple sclerosis. Reviews[1,2] and a meta-analysis[3] of controlled studies of glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis concluded that it is of benefit, although one systematic review[4] questioned this and failed to find evidence to support its routine use. It also produced similar results to interferon beta-1b in a comparative study[5] that assessed disease activity through monthly MRI scans for up to 2 years. Early treatment with glatiramer acetate in patients with clinically isolated syndrome who are at risk of developing multiple sclerosis significantly reduced the frequency of conversion to clinically definite disease and delayed the occurrence of a second attack.[6]

The mechanism of action of glatiramer acetate has also been reviewed.[7,8]

1. Simpson D, *et al.* Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis. *CNS Drugs* 2002; 16: 823–50.
2. Ruggieri M, *et al.* Glatiramer acetate in multiple sclerosis: a review. *CNS Drug Rev* 2007; 13: 178–91.
3. Boneschi FM, *et al.* Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. *Multiple Sclerosis* 2003; 9: 349–55.
4. Munari L, *et al.* Therapy with glatiramer acetate for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/01/08).
5. Cadavid D, *et al.* Efficacy of treatment of MS with IFN β -1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology* 2009; 72: 1976–83.
6. Comi G, *et al.* Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1503–11.
7. Schrempf W, Ziemssen T. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Autoimmun Rev* 2007; 6: 469–75.
8. Racke MK, *et al.* The mechanism of action of glatiramer acetate treatment in multiple sclerosis. *Neurology* 2010; 74 (suppl 1): S25–S30.

Adverse Effects and Precautions

Immediate post-injection reactions are common with glatiramer acetate and include chest pain, palpitations or tachycardia, dyspnoea, throat constriction, urticaria, flushing (vasodilatation), and anxiety. These reactions are generally short-lived and resolve spontaneously. They have generally occurred only some months after treatment with glatiramer was started. Other common adverse effects include asthenia, nausea, vomiting, constipation, rash, arthralgia, back pain, and dizziness. Convulsions and anaphylactoid reactions have been reported rarely.

Antibodies to the drug develop with chronic therapy but are of unknown clinical significance. Pain, erythema, inflammation, mass, pruritus, and induration may occur at the injection site; localised lipoatrophy and, rarely, skin necrosis has also been reported.

Glatiramer acetate should be given with caution to patients with pre-existing cardiac disorders; such patients should be followed up regularly during treatment.

References.
1. Ziemssen T, *et al.* Risk-benefit assessment of glatiramer acetate in multiple sclerosis. *Drug Safety* 2001; 24: 979–90.

Anaphylaxis. A systemic anaphylactic reaction to glatiramer acetate developed in a patient who showed a strong immunoglobulin response including specific immunoglobulin E.[1]

1. Rauschka H, *et al.* Severe anaphylactic reaction to glatiramer acetate with specific IgE. *Neurology* 2005; 64: 1481–2.

Effects on the skin. Localised lipoatrophy at the injection site developed in 6 patients receiving glatiramer acetate.[1] Examination of 76 patients over a 6-month period in one centre[2] revealed evidence of lipoatrophy in at least one injection site in 34 patients; of these, 5 cases were severe. Prevalence of lipoatrophy was much higher than expected, and in some cases, it occurred only a few months after treatment started.[2]

Erythema nodosum confirmed by biopsy has been reported in one patient;[3] spontaneous resolution occurred without stopping treatment.

1. Drago F, *et al.* Localized lipoatrophy after glatiramer acetate injection in patients with remitting-relapsing multiple sclerosis. *Arch Dermatol* 1999; 135: 1277–8.
2. Edgar CM, *et al.* Lipoatrophy in patients with multiple sclerosis on glatiramer acetate. *Can J Neurol Sci* 2004; 31: 58–63.
3. Thouvenot E, *et al.* Erythema nodosum and glatiramer acetate treatment in relapsing-remitting multiple sclerosis. *Multiple Sclerosis* 2007; 13: 941–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glatiramer acetate 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 31/10/11)

Interactions

UK licensed product information reports that an increased incidence of injection-site reactions to glatiramer acetate has been seen in patients also given corticosteroids.

Pharmacokinetics

A substantial fraction of a subcutaneous dose of glatiramer is believed to be hydrolysed locally. Some of the injected dose is also presumed to enter the lymphatic system, either intact or partially hydrolysed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Copaxone; *Austral.*: Copaxone; *Austria*: Copaxone; *Belg.*: Copaxone; *Braz.*: Copaxone; *Canad.*: Copaxone; *Cz.*: Copaxone; *Denm.*: Copaxone; *Fin.*: Copaxone; *Fr.*: Copaxone; *Ger.*: Copaxone; *Gr.*: Copaxone; *Hung.*: Copaxone; *Irl.*: Copaxone; *Israel*: Copaxone; *Ital.*: Copaxone; *Mex.*: Copaxone†; *Neth.*: Copaxone; *Norw.*: Copaxone; *NZ*: Copaxone; *Pol.*: Copaxone; *Port.*: Copaxone; *Rus.*: Copaxone (Копаксон); *S.Afr.*: Copaxone; *Spain*: Copaxone; *Swed.*: Copaxone; *Switz.*: Copaxone; *Turk.*: Copaxone; *UK*: Copaxone; *Ukr.*: Copaxone (Копаксон); *USA*: Copaxone.

Glicofosfopeptical

AM-3; Fosfoglicopeptical; Glycophosphopeptical; Immunoferon; Иммуноферон.
CAS — 87139-86-4.

Profile

Glicofosfopeptical is a polysaccharide-protein complex that is reported to possess immunostimulant properties. It has been given orally in doses of 1 g every eight hours.

References.
1. Alvarez-Mon M, *et al.* Treatment with the immunomodulator AM3 improves the health-related quality of life of patients with COPD. *Chest* 2005; 127: 1212–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Inmunol; *Port.*: Imunoferon; *Spain*: Inmunoferon.

Glucomannan

E425; Glucomanano; Harina de Konjac; Konjac Flour; Konjac Mannan; Глюкоманнан.
UNII — 36W3E5TAMG.

Profile

Glucomannan, a powdered extract from the tubers of *Amorphophallus konjac*, has been promoted as an anorectic. It has been claimed to reduce the appetite by absorbing liquid in the gastrointestinal tract. It is also used in the treatment of constipation and hyperlipidaemia. Glucomannan has been investigated as a dietary adjunct in the management of diabetes mellitus.

There is a risk of intestinal or oesophageal obstruction and faecal impaction, especially if it is swallowed dry. Therefore, it should always be taken with sufficient fluid and should not be taken immediately before going to bed. It should be avoided in patients who have difficulty swallowing.

References.
1. Henry DA, *et al.* Glucomannan and risk of oesophageal obstruction. *BMJ* 1986; 292: 591–2.
2. Renard E, *et al.* Noninsulin-dependent diabetes and glucose intolerance: effect of glucomannan fibre on blood glucose and serum insulin. *Sem Hop Paris* 1991; 67: 153–7.
3. Vuksan V, *et al.* Beneficial effects of viscous dietary fiber from konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. *Diabetes Care* 2000; 23: 9–14.
4. Staiano A, *et al.* Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. *J Pediatr* 2000; 136: 41–5.
5. Loening-Baucke V, *et al.* Fiber (glucomannan) is beneficial in the treatment of childhood constipation. Abstract: *Pediatrics* 2004; 113: 259. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e259.pdf (accessed 16/08/10)
6. Keithley J, Swanson B. Glucomannan and obesity: a critical review. *Altern Ther Health Med* 2005; 11: 30–4.
7. Vanderbeek PB, *et al.* Esophageal obstruction from a hygroscopic pharmacobezoar containing glucomannan. *Clin Toxicol* 2007; 45: 80–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Dietmann; *Ital.*: Cadicioc; Dicoplus; Dietoman; NormaLine; *Mex.*: Dietoman; Esbeltex; *Singapore*: Dulcofibre.

Multi-ingredient Preparations. *Arg.*: Adelgacin; Green Diet; KLB6 Fruit Diet; *Chile*: Delgadol Fibra; *Fr.*: Filigel†; *Ital.*: Agioslim; Ecamannan; Fibrovit; Glucoman; Lactomannan; *Philipp.*: Thinber Fiber Complex†.

Gluconic Acid

Dextronic Acid; E574; Glycogenic Acid; Maltonic Acid; Pentahydroxycaproic Acid; Глюконовая Кислота.
D-Gluconic acid.
$C_6H_{12}O_7$=196.2
CAS — 526-95-4.
UNII — R4R8J0Q44B.

Gluconolactone

E575; Glucono delta-lactone; Glucono-delta-lactone; 1,5-Gluconolactone; D-Glucono-1,5-lactone; Глюконолактон.
D-Gluconic acid δ-lactone.
$C_6H_{10}O_6$=178.1
CAS — 90-80-2.
UNII — WQ29KQ9POT.

Pharmacopoeias. In *US*.

USP 36: (Gluconolactone). A fine, white, practically odourless, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Profile

Gluconolactone is hydrolysed to gluconic acid, a polyhydroxy acid. It has similar properties to the alpha hydroxy acids glycolic acid (p. 1704.3) and mandelic acid (p. 320.3) and has been used in skin disorders and for urinary catheter care. Gluconolactone and gluconic acid are also used as food additives.

References.
1. Grimes PE, *et al.* The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* 2004; 73 (suppl 2): 3–13.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Arg.*: Neoceuticals Gel de Limpieza Facial; NeoStrata; *Austral.*: NeoStrata; *Canad.*: NeoStrata†; *Chile*: NeoStrata; NeoStrata; NeoStrata; Teen Derm K; *Fr.*: Ruboderm; *Indon.*: Hidrogel†; *Turk.*: NeoStrata; *UK*: Uriflex R; Uro-Tainer Solution R; *USA*: Renacidin.

Glucosamine *(USAN, rINN)*

Chitosamine; Glucosamina; Glucosaminum; NSC-758; Глюкозамин.
2-Amino-2-deoxy-β-D-glucopyranose.
$C_6H_{13}NO_5$=179.2
CAS — 3416-24-8.
ATC — M01AX05.
ATC Vet — QM01AX05.
UNII — N08U5BOQ1K.

Glucosamine Hydrochloride *(rINN)*

Chitosamine Hydrochloride; Glucosamina, hidrocloruro de; Glucosamine, Chlorhydrate de; Glucosamini Hydrochloridum; Glukozaminy chlorowodorek; Hidrocloruro de glucosamina; Глюкозамина Гидрохлорид.
$C_6H_{13}NO_5.HCl$=215.6
CAS — 66-84-2.
UNII — 750W53330FY.

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

Ph. Eur. 8: (Glucosamine Hydrochloride). It is isolated from natural sources or produced by fermentation. A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 3.0 to 5.0.

USP 36: (Glucosamine Hydrochloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Potassium Chloride

$(C_6H_{14}NO_5)_2SO_4.2KCl$=605.5

Pharmacopoeias. In *US*.

USP 36: (Glucosamine Sulfate Potassium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Glucosamine Sulfate Sodium Chloride

$(C_6H_{14}NO_5)_2SO_4.2NaCl$=573.3

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

Ph. Eur. 8: (Glucosamine Sulfate Sodium Chloride). It is prepared from glucosamine hydrochloride isolated from natural sources or produced by fermentation, and sodium sulfate. A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 3.0 to 5.0.

USP 36: (Glucosamine Sulfate Sodium Chloride). A 2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Uses and Administration

Glucosamine is a natural substance found in chitin, mucoproteins, and mucopolysaccharides. It is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue in the body; glucosamine is also present in tendons and ligaments. Glucosamine must be synthesised by the body but the ability to do this declines with age. Glucosamine has therefore been given for its supposed chondroprotective action in musculoskeletal and joint disorders including osteoarthritis (see below). Glucosamine may be isolated from chitin or prepared synthetically; it has also been given as the hydrochloride, sulfate, and hydroiodide salts, or as complexes such as glucosamine sulfate potassium chloride, glucosamine sulfate sodium chloride, and glucosamine hydrochloride magnesium sulfate.

Osteoarthritis. Glucosamine and its salts are widely available as licensed products or so-called 'health supplements' used for the management of osteoarthritis (p. 12.3); they may be combined with other substances supposed to be of benefit, including chondroitin (p. 2476.1), vitamins, and various herbs. Meta-analyses[1,2] of randomised placebo-controlled studies concluded that while there was some evidence for efficacy of glucosamine and chondroitin in the treatment of osteoarthritis, methodological flaws and publication bias had led to exaggeration of its potential benefit,[1] and that further studies are needed to fully characterise their disease-modifying properties.[2] A systematic review[3] of the use of glucosamine for osteoarthritis that included later controlled studies concluded that glucosamine is as safe as placebo but there was little evidence of improvement in pain or function. A further randomised controlled study[4] in 222 patients with hip osteoarthritis found no benefit after treatment with glucosamine for 2 years compared with placebo, and a meta-analysis[5] of controlled studies of chondroitin for osteoarthritis of the knee or hip concluded that chondroitin had minimal or no ben-

efit. Further research is needed to confirm whether there are differences in efficacy between glucosamine salts, preparations, or routes, and when used with other agents (e.g. chondroitin) or in different patient subgroups.[3] A large multicentre double-blind study[6] in 1583 patients with symptomatic knee osteoarthritis to compare glucosamine and chondroitin, either alone or in combination, found no clear evidence of benefit in pain reduction compared with placebo or celecoxib, although there was a tendency to more positive results in a subset of patients with moderate to severe knee pain. An evidence-based report[7] into the use of complementary medicines to treat rheumatic diseases concluded that despite some mixed results, the majority of controlled studies of glucosamine sulfate showed significant clinical benefit whereas the evidence for glucosamine hydrochloride was either unavailable or less convincing. For chondroitin, the evidence from controlled studies was inconsistent, although the majority showed significant clinical benefit for pain reduction.

1. McAlindon TE, *et al.* Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000; **283**: 1469–75.
2. Richy F, *et al.* Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003; **163**: 1514–22.
3. Towheed T, *et al.* Glucosamine therapy for treating osteoarthritis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2005 (accessed 14/05/08).
4. Rozendaal RM, *et al.* Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008; **148**: 268–77.
5. Reichenbach S, *et al.* Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007; **146**: 580–90.
6. Clegg DO, *et al.* Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; **354**: 795–808.
7. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)

Adverse Effects and Precautions

Effects on glucose metabolism. Glucosamine has a role in glucose metabolism, increasing insulin resistance in skeletal muscle,[1,2] and this has raised concerns about its safety profile in diabetic patients.[3] However, alteration of glycaemic homoeostasis was not found in a 3-year randomised controlled study in patients without diabetes.[4] A review[5] of the literature found limited data on diabetic patients taking glucosamine supplements, and recommended close monitoring of blood glucose levels in this group until more data are available.

1. Adams ME. Hype about glucosamine. *Lancet* 1999; **354**: 353–4.
2. Chan NN, *et al.* Drug-related hyperglycemia. *JAMA* 2002; **287**: 714–15.
3. Chan NN, *et al.* Glucosamine sulphate and osteoarthritis. *Lancet* 2001; **357**: 1618–9.
4. Reginster JY, *et al.* Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; **357**: 251–6.
5. Stumpf JL, Lin SW. Effect of glucosamine on glucose control. *Ann Pharmacother* 2006; **40**: 694–8.

Effects on the skin. The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] has received 51 reports of allergic skin reactions with glucosamine, including erythematous rash, angioedema, urticaria, rash, and pruritus. It was noted that some preparations contain glucosamine sourced from seafood and therefore people with an allergy to shellfish may be at greater risk for hypersensitivity reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Skin reactions with glucosamine. *Aust Adverse Drug Reac Bull* 2005; **24**: 23. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0512.pdf (accessed 14/05/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glucosamine 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 20/10/11)

Interactions

For reference to the effect of glucosamine on warfarin, see Dietary Supplements under Interactions of Warfarin, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Adaxil; Artrilase; Asoglutan; Baliartrin Potasico; Baliartrin; Belmalen Plus; Findol; Gluco Arrumalon; Glucometil K; Glucotrin Flex; Glucotrin Pro-Flex; Mecanyl K; Mecanyl; Ostatac; Pertinar; Vartalon Complemento; Vartalon K; *Austral.*: GenFlex†; Joints in Motion; PM Joint-Aid†; *Austria*: Dona; Flexove; Progona; *Belg.*: Dolenio; Donacom; Voltaflex†; *Braz.*: Artoglico; Dinaflex; Faximin; Glucoreumin; Injeflex; Ortosamin; Suligic; *Chile*: Artridol; Bioflex†; Dinaflex; Reufin; *China*: Bao Jie Li (保节力); Bu Mai Xin (步迈新); Duan Zheng (增正); Jiu Li (九力); Liu Pu An (留普安); Peitil (培古立); Pu Li (普立); Pu Li De (普力得); Viartril S (维固力); Wei Er Gu (维尔固); Yi Suo Jie (伊索佳); *Cz.*: Bayflex; Chondrostad; Dona; Flexove; Gool; Mediflex†; Voltadyn†; *Denm.*: Dolenio; Giscosamine; Glucomed†; Perigona; *Fin.*: Arthrimel; Arthryl; Comfora; G-Lenk†; Glucadol; Glucorix; Glucosine; Perigona; *Fr.*: Dolenio; Flexea; Osaflexan; Oscart†; Structoflex; Voltaflex; *Ger.*: Dona; Leka; Mobilat Glucosamin†; Progona; Voltaflex†; *Gr.*: Anarthril; Arthroloc; Best; Dolenio; Donamin; Donarot; Donarthril; Effer-Activ; Elimer; Energorot; Fragilis; Gioral; Glucasulf; Glucosamil; Glucozant; Glukotral; Gluminal; Glunarot; Glusamon; Gluvedus; Glycefort; Laraned; Lasanol; Lipathrec; Medomin; Minedon; Nerita; Painoff; Recosine; Sacrum; Samiclar; Sufigal; Taredon; Viartril; Viremax; Voltaflex; Xanalife; Zacosteo; *Hong Kong*: Arthritil†; Aussamin; Cartril-S; Chitaq; Doctor's Choice for Joints; Donna†; F-Vialin†; MarinEx; Vialbone†; Viartril S; Vidatril†; Vitoport; Vocarril; Voltaflex; *Hung.*: Dona; Gool; *India*: Artica; Cartiel; Cartigen; Cartilamine; Diemann; Flextra; Glucart; Glucosam; Jointace; Kondro-OD; Lubrijoint; Osicare-DS; *Indon.*: Cartos; Fitbon; Mediflex; Oste OD; Reflexor; *Irl.*: Arthriaid; Arthrimel; Dolenio; Dona; Glusamin; Osteoeze; Osteole; Viartril S; *Israel*: Arthryl; *Ital.*: Dona; Glexar; Minarex; Xicil; *Malaysia*: Artril; Artronil; Cartril-S; Cosamine†; Coxium; Donna; Flexsa; Osteofree; Procosa†; Viartril S; *Mex.*: Artriman; Faximin; Flaxblutriz; Vartalon; *Neth.*: Cartimin; Dolenio; Donacom; Glucofleks†; Glucomed; Voltaflex Glucosamine; *Norw.*: Donacom; Gluxine†; Movere†; Perigona; Samin; *Philipp.*: Cartrosyn; Flexsa; Glucart; Poly-Nag†; Sancom; Synotec; Viartril S; *Pol.*: Actistav; Arthryl; Flexove; *Port.*: Arthramina†; Dolenio; Glarzena; Glucomed; Glucosine; Glufan; Glusina; Minitil; Rieg†; Viartril S; *Rus.*: Dona (Дона); Elbona (Эльбона); Pharmaskin (Фармаскин); *Singapore*: ArthriCare; Artril†; Artrilase; Artronil†; Cartril-S†; Coxium; Flexsa; Gluco-S; Glutilage; Olivenol Livin' Active; Osteofree; Viartril S; Vital; *Spain*: Acenam; Arafisio; Cartisorb; Coderol; Glucomed†; Glufan; Gluniro; Hespercorbin; Mascartil; Xicil; *Swed.*: Artrox; Comfora; Donacom†; Glucomed; Giucosine; Perigona; *Switz.*: Voltaflex†; *Thai.*: Arthro-S; Artronil; Athril; Bio-Glucosamine; Biotril-s; BOS; Caseal; Coxium; Cuine; Flexsa; Gaxium; Gluco-S; Glucosa; Glucosamate; Glucotril; Glumesa; Glusa†; Glusafex; Glusamine†; Kosamine; Osamine; Prosulf; Rheutril; Viaflex; Viartril S; Viartril S; Zynotril; *Turk.*: Dona; *UK*: Alateris; Dolenio; Flexeze; Flexi-Melt; Glusartel; Joint-e-Licious; *Ukr.*: Arthron Flex (Артрон Флекс); Artiflex (Артифлекс); Dona (Дона); Flex-A-Min Glucosamin (Флекс-А-Мин Глюкозамин)†; Sinarta (Синарта); *Venez.*: Vartalon; Viartril S.

Multi-ingredient Preparations. *Arg.*: Adaxil Forte; Adaxil Plus; Artrilase Complex; Artrocaptin; Asotrex; Baliartrin Duo; Cartiburon Flex; Cartiflex Forte; Dolo Asotrex; Dolo Baliartrin; Ecosamina; Etinox; Etinox; Finartrit; Findol Plus; Gluco Arrumalon Duo; Glucobefol†; Glucocartiflex; Glucometil 3; Glucometil K Duo; Glucometil Plus; Glucosamina Sport; Glucotrin Forte; Glucotrin VL; Mecanyl Duo; Mecanyl K Duo; Nectar G; Ostatac Duo; Reumosan Compuesto; Sigmaflex; Vartalon Duo K; Vartalon Duo; *Austral.*: AB Ausbiobone; AB Carsa Giox; AB Oriostin; Accelerex; Arthro-Eze; Bioflex†; Bonlutin; Formula for Joints; Full Motion; GenFlex 3†; GenFlex NKO†; GenFlex Plus†; Joint Ease; Joint Formula Advanced with MSM Booster; Joint Formula Advanced; Joint Mobility†; MeticGlucotin; Osteo-Relief Plus MSM; Osteo-Relief; OsteoEze Active + MSM; OsteoEze Active; OsteoEze Bone & Joint; PM Joint-Care; PM Metic-Glucotin; *Braz.*: Artrolive; Condroflex; *Canad.*: Procosa; Restorativ Glucosamine Muscle and Joint; *Chile*: Artridol Duo; Dinaflex Duo; Eniflex Duo; Euroflex; Flexure; Hiperflex; Osteo Bi-Flex†; *China*: Ai Mei Xing (爱美辛); *Fr.*: Arthrobiane; Capsaine; Chondrosteo; Cicatendon; Cuivramine; Dexsil Articulations; Dexsil Sport; Fleximax; Glucarthroz; Kinesamine; Rhumadol; Synotabs; *Hong Kong*: Arthritil Plus†; Doctor's Choice Fortified Joint Support†; Procosa II†; *Hung.*: Porcerosito; *India*: Admine; Alnamax-G; Altocerin-GM; Arth; Arthar; Artheal; Arthocare DS; Arthocare; Arthocerin-G; Arthodia-G; Arthrovit Plus; Artiflx; Baknil; Bigjoint; Bonit Join; Bonjo Aid; Carticare; Cartiflx; Cartigen Plus; Cartigen; Cartilamine DS; Cartilamine Forte; Cartilamine Total; Cartilamine-SR; Cartimost GM; Cartipro; Cartisafe; Cartisark; Cartispan; Cartivit; Cartiwel; Cartiz-GM; Cartiz; Cartizole Plus; Cartup; Compensate; Conjoint; Cool-Joint; Cool-Joint; Cosa-G; Cosantin; Dicimax-G; Difirin Plus; Dims-GM; DN Plus; Durajoint-GM; Dycerin-GM; Flexi Cap; Flexibel; Flextra-D; Free M; Freeflex; Fremov-ME; Fremov; GC Flex; Gencart; Glortho Forte; Glucomade-500; Glucomade; Glucovit Plus; Glutin; GSO4; Icerin-GM; Intecar; Jaizzy-GM; Joint Guard; Jointace Forte; Jointace-DN; Jointop; Jonty; Kalhar; Kondro; Lecerein-GM; Lefax-G; Mecocas-Ortho; Mega Freeflex; Mericart; Mobijoint; Mycer G; Necare; Neuromed; Nucart-OA; Nurokind Ortho; OA Plus; Orbone Forte; Orbone; Ordi-G; Orthocerin-G; Osicare; Ostakair; Ostawin; Osteocip; Osteoflex; Osteojoin-D; Ostifin-G; Ostiwel Forte; Ostiwel; Ostodia-G; Ostofit; Ostop; Ostovit-G; Ostovit; Pacto-GMD; *Indon.*: Aptivium Optimum Joint Formula†; Artriox†; Artritin; Artro Plus; Artro; Aviter; Bonic Plus; Bonic; Bonilav; Cartiflex; Cartin; Chondro-PA; Fitajoint; Fitbon Plus; Flexor; Pripos; GCM; Joint Care Plus; Joint Care; Jointace; Jointfit; Jointfit; Jointfit; Lavarix; Maxitrin†; Naturema; Nutrijoint; OA Forte; OA Plus; OA; Osamin; Ositin; Osmetin 3; Oste; Ostela; Osteoflam; Osteokom Forte; Osteokom; Osteokom; Osteonic; Osteor Plus; Osteor-C; Osteor; Osteotin; Ostine; Ostrimix; Osvion Plus; Rebone; Rheumatin Forte; Rheumatin; Risteon; Triflexor; Triostee; Viopor-M Forte; Viopor-M; Viopor; Viostin Com DS; Viostin Com; Viostin-X; Viusid; Vostem; Vosteon; *Irl.*: Seven Seas Active Sport†; *Israel*: Mega Gluflex with MSN; Mega Gluflex; *Ital.*: Cartago; Cartijoint†; Condrorexil; Fitogenase; Ginepausil; Joint Support; Osteoclar; Reumil; Reumilase Plus; Reumilase SD; Reumilase; Synchrocell; Vitreoclar Crono; Vitreolux; *Malaysia*: Conart; Cosamine Plus; *Mex.*: Actiman; Artiflex; Artrifar; Mex-Amina; Procosa II; Vartalon Compositum; *Mon.*: Algicuivre; *Philipp.*: Artiflex; Cartifast-C; Flexxibon; Osteoaid; Ruflex; *Port.*: Synchrocell; Synchrovit; *Rus.*: Artra (Артра); KONDROnova (КОНДРОнова); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); *S.Afr.*: ProFLEX 750†; ProFLEX†; *Singapore*: Arthro-Flex; Articolase (w/glucosamine); Artril G†; Artrilase; Cartipro; Glucocal; Glutilage Plus; Joint Care; JointFlex; Procosa II†; Ruflex; Scar Esthetique; Seven Seas JointCare Max; Seven Seas JointCare; *Spain*: Droglican; *Thai.*: Artrofort Complex; *Turk.*: Jointace; Ultimate; *UK*: Arheumacare; BackOsamine; Flexeze; GlucOsamax; GlucoSelene; Healtheries Musseltone & Glucosamine; Joint Action; Jointace; Jointace; Jointace; JointCare Max; *Ukr.*: Arthron Complex (Артрон Комплекс); Arthron-Triactive (Артрон Триактив); Artritosamin (Артритозамин); Chondroitin Complex (Хондроитин Комплекс); Flex-A-Min Complex (Флекс-А-Мин Комплекс)†; Hondra-Syla (Хондра-Силя); Movex Active (Мовекс Актив); Movex Comfort (Мовекс Комфорт); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Osteoartisi Max (Остеоартизи Макс); Theraflex (Терафлекс); Theraflex Advance (Терафлекс Адванс); Theraflex M (Терафлекс М); *USA*: Arthritis Free; Cosamin; Dorofen; Duraflex Comfort; Stopain Cold Extra Strength; *Venez.*: Artrosamin.

Pharmacopoeial Preparations

USP 36: Glucosamine and Chondroitin Sulfate Sodium Tablets; Glucosamine and Methylsulfonylmethane Tablets; Glucosamine Tablets; Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets.

Glucose Oxidase *(USAN)*

Corylophyline; EC 1.1.3.4; β-D-Glucopyranose aerodehydrogenase; Glucosa oxidasa; GO; Microcide; Notatin; P-FAD; Глюкооксидаза.

CAS — 9001-37-0.
UNII — 0T8392USN1.

Profile

Glucose oxidase is an enzyme obtained from certain fungi that catalyses the oxidation of glucose to gluconic acid with the concomitant production of hydrogen peroxide. It is used for its preservative properties as an additive in certain foods, sometimes with catalase (p. 2472.2). It is also used in fertility tests and tests of diabetic control. It has been used as an ingredient of topical oral preparations for the treatment of dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Flaminal; *Singapore*: Biotene†; Biotene; Biotene; OralSeven; OralSeven; OralSeven; *UK*: Biotene Dry Mouth; Biotene Oralbalance; Flaminal; *USA*: Biotene with Calcium.

Pharmacopoeial Preparations

USP 36: Glucose Enzymatic Test Strip.

Glucose Tests

Glucosa, pruebas de.

Profile

Several tests are available so that patients with diabetes mellitus (p. 461.1) can monitor their disease. Tests can be used to detect the presence of glucose in the urine and some of the preparations are used to detect several substances in the urine. These tests are easy to carry out but are not considered reliable enough for insulin-dependent patients who should ideally check their blood-glucose concentrations using one of the available blood tests. Diabetic clinics often measure the degree of haemoglobin glycation (HbA_{1c}) as an indicator of mean blood-glucose control over a period of weeks or months.

Urine tests generally use either the copper-reduction method or the glucose-oxidase method and both produce a colour change in the presence of glucose. Blood tests generally use the glucose-oxidase method; they may be read visually or by means of a meter. A meter gives the more precise reading. Patients should be properly trained in the use of these tests and in the interpretation of the results; they should be aware that concomitant drug therapy might affect the result.

Precautions. Preparations that contain, or are metabolised to, maltose (p. 2081.1), galactose (p. 1588.1), or xylose (p. 2649.2) may interfere with the results from glucose tests based on dehydrogenase pyrroloquinolinequinone

(GDH-PQQ) monitoring systems as these are non-specific for glucose. Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. MHRA. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Accu-Chek; Accutrend Glucosa; Achtung; Ascensia; Betachek; Contour TS; Dextrostix; Diastix; Elite†; Glucostix; One Touch; Precision Plus; Prestige; Prodigy Autocode; Sure Step; *Austral.*: Accu-Chek; Ascensia†; Betachek; BM-Test BG†; BM-Test Glycemie 20-800†; Clinistix†; Clinitest†; Diabur-Test 5000†; Diastix; Esprit†; Glucoflex-R; Glucostix; Glucotrend†; Medi-Test Glucose†; Omnitest; Optium; Precision Plus†; *Braz.*: Accu-Chek; Accutrend†; Glicofita Plus†; Haemo-Glukotest†; *Canad.*: Accu-Chek†; Ascensia Elite; Chemstrip bG†; Clinistix†; Clinitest†; Diastix†; One Touch†; Sof-Tact†; *Chile*: Accu-Chek; Accutrend Glucosa†; Ascencia; Contour; Major II; *Fr.*: Accu-Chek; Ascensia; Caresens N; Glucomen†; Medisense†; One Touch; *India*: Diastix†; Haemo-Glukotest; *Irl.*: Accu-Chek; BM-Accutest†; Clinistix†; Clinitest†; Combina Glucose; Diabur-Test 5000†; Diastix; Freestyle†; Glucomen†; Glucometer Elite†; Glucostix†; Glucotide†; One Touch†; PocketScan†; *Ital.*: Accu-Chek; Accutrend Glucose; Ascensia; Clinistix; Clinitest; Diabur-Test 5000; Diastix; Euroflash; EZ Smart; Finetouch; Freestyle; Glucocard; Glucoscan; One Touch; Optium Plus; Uni-Check†; *Mex.*: Accu-Chek; Accutrend Glucose†; Clinitest; Dextrostix; Diabur-Test 5000†; Diastix; Haemo-Glukotest 20-800†; *NZ*: Accu-Chek; Clinistix†; Clinitest†; Diabur-5000†; Diastix†; *Port.*: Clinistix†; Glucocard†; Glucodisc; Glucostix†; One Touch; *UK*: Ascensia Glucodisc; BM-Accutest; BM-Test 1-44; Breeze 2; Clinistix; Clinitest; Contour; Diabur-Test 5000; Diastix; ExacTech; Freestyle; Glucoflex-R; Glucomen; Hypoguard Supreme Plus; Medi-Test Glucose; Medisense; Optium Plus; *USA*: Accu-Chek Advantage; Choice DM; Diascan; First Choice; Glucofilm; Glucostix; One Touch.

Pharmacopoeial Preparations

USP 36: Glucose Enzymatic Test Strip.

Glucuronic Acid

Глюкуроновая Кислота.

D-Glucuronic acid.

$C_6H_{10}O_7$=194.1

CAS — 576-37-4 (DL-glucuronic acid); 6556-12-3 (D-glucuronic acid).

UNII — 8A5D83Q4RW.

Glucurolactone *(rINN)*

Glucurolactona; Glucurolactonum; D-Glucuronic Acid Lactone; Glucuronolactone; Глюкуролактон.

D-Glucofuranuronic acid γ-lactone.

$C_6H_8O_6$=176.1

CAS — 63-29-6; 32449-92-6.

UNII — XE4Y3016M9.

Glucuronamide *(BAN, rINN)*

Glucuronamida; Glucuronamidum; Глюкуронамид.

β-D-Glucopyranuronamide.

$C_6H_{11}NO_6$=193.2

CAS — 3789-97-7 (glucuronamide); 3574-23-0 (D-glucuronamide); 61914-43-0 (β-D-glucuronamide).

UNII — 1Q5MP1Z8HW.

Sodium Glucuronate

Sodu glukuroniań; Глюкуронат Натрия.

$C_6H_9NaO_7$=216.1

CAS — 14984-34-0.

UNII — 631391W27S.

Profile

Glucuronic acid is one of the components of hyaluronic acid (p. 2526.2) and also has an important role in the metabolism of many endogenous substances, drugs, and toxins. It has been used topically as a potential precursor of hyaluronic acid, and has also been used as a nutritional supplement. Glucuronamide, glucurolactone (glucuronic acid lactone), diolamine glucuronate, and other glucuronates have also been used as supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Qi Gu Le (奇谷乐); Wei Mei Le (唯每乐); Xiu Fu (休孚); You Ni Kai (尤尼凯).

Multi-ingredient Preparations. *Arg.*: Stimulnerv; *Belg.*: Guronsan†; *Fr.*: Guronsan; Sarvit a la glucuronamide†; *Hong Kong*: Jetepar†; *Ital.*: Reumilase; Synchrocell; *Malaysia*: Jetepar; *Philipp.*: Jetepar; *Port.*: Guronsan; Synchrocell; Synchrovit; *S.Afr.*: Guronsan C; *Singapore*: Jetepar†; *Spain*: Guronsan†.

Gluten

Глютен.

UNII — 1534KB653J (wheat gluten).

Profile

Gluten is a mixture of 2 proteins, gliadin and glutenin, and is present in wheat flour and to a lesser extent in barley and rye. Gliadin is a prolamine, one of the 2 chief groups of plant proteins, and glutenin belongs to the other main group termed glutelins.

Gluten is of medicinal and pharmaceutical interest in that patients with coeliac disease (p. 2043.1) are sensitive to the protein fraction of gluten contained in the normal diet. Treatment consists of the use of gluten-free diets; gluten-free foods are available.

A gluten-free diet may also be beneficial in patients with dermatitis herpetiformis (p. 1683.2).

Glycerol *(rINN)* ⊗

E422; Glicerin; Glicerina; Glicerol; Glicerolis; Glisein; Gliserol; Glisin; Glycerin; Glycerine; Glycerol; Glycerolum; Glyseroli; Глицерол.

Propane-1,2,3-triol.

$C_3H_8O_3$=92.09

CAS — 56-81-5.

ATC — A06AG04; A06AX01.

ATC Vet — QA06AG04; QA06AX01; QA16QA03.

UNII — PDC6A3C0OX.

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

Eur. and *Int.* also include Glycerol (85 per cent).

Ph. Eur. 8: (Glycerol). A clear, colourless or almost colourless, very hygroscopic, syrupy liquid, unctuous to the touch. Miscible with water and with alcohol; slightly soluble in acetone; practically insoluble in fixed oils and in essential oils. Store in airtight containers.

USP 36: (Glycerin). A clear, colourless, hygroscopic, syrupy liquid. Has not more than a slight characteristic odour, which is neither harsh nor disagreeable. Miscible with water and with alcohol; insoluble in chloroform, in ether, and in fixed and volatile oils. Its solutions are neutral to litmus. Store in airtight containers.

Incompatibility. Strong oxidising agents form explosive mixtures with glycerol. Black discoloration has been reported with glycerol and bismuth subnitrate or zinc oxide when exposed to light.

Sterilisation. Sterilisation of glycerol by membrane filtration is described.[1]

1. McCluskey SV. Sterilization of glycerin. *Am J Health-Syst Pharm* 2008; 65: 1173–6.

Uses and Administration

Glycerol is an osmotic dehydrating agent with hygroscopic and lubricating properties. When given orally or parenterally, glycerol increases the plasma osmolality, resulting in the movement of water by osmosis from the extravascular spaces into the plasma.

Glycerol is given orally for the short-term reduction of vitreous volume and intra-ocular pressure before and after ophthalmic surgery, and as an adjunct in the management of acute glaucoma (p. 1999.1). Its onset of action is rapid, with a maximal reduction in intra-ocular pressure occurring about 1 to 1½ hours after a dose; the duration of action is about 5 hours. The usual initial dose of glycerol is 1 to 1.8 g/kg given as a 50% solution. There can be problems of palatability when glycerol solutions are given orally; chilling or flavouring the solutions may help.

Glycerol may be applied topically to reduce corneal oedema, but as the effect is only transient its use is largely limited to an adjunct in eye examination and diagnosis. Glycerol eye drops can be painful on instillation and use of a local anaesthetic beforehand has been recommended.

Glycerol has also been given orally or intravenously to reduce intracranial pressure (see below).

Glycerol may be used rectally as suppositories or a solution in single doses to promote faecal evacuation in the management of constipation (p. 1804.3). It usually acts within 15 to 30 minutes. Glycerol is commonly classified as an osmotic laxative but may act additionally or alternatively through its local irritant effects; it may also have lubricating and faecal softening actions.

Glycerol is used as a demulcent in cough preparations (p. 1651.2).

Glycerol has many applications in pharmaceutical formulation; these include its use as a vehicle and solvent, as a sweetening agent, as a preservative in some liquid medications, as a plasticiser in tablet film-coating, and as a tonicity adjuster. It is often included in topical preparations such as eye drops, creams, and lotions as a lubricant and also for its moisturising properties since, when absorbed, its hygroscopic action can enhance moisture retention. Ear drops for the removal of ear wax often contain glycerol as a lubricating and softening agent.

Glycerol is also used as a cryoprotectant in cryopreservation.

Diagnosis of Ménière's disease. Glycerol has been used[1] in the diagnosis of Ménière's disease (p. 611.2) to distinguish potentially reversible cochlear dysfunction from the relatively irreversible pathology of advanced disease, or to predict the results of endolymphatic sac surgery. Glycerol is given orally to reduce the endolymphatic fluid volume and pressure and any transient improvement in hearing is measured. However, the adverse effects of glycerol such as headache, nausea, and vomiting can be a problem and the test has been reported to have low sensitivity and to give false-positive results. See also under Effects on the Ears, p. 2518.1.

1. Skalabrin TA, Mangham CA. Analysis of the glycerin test for Meniere's disease. *Otolaryngol Head Neck Surg* 1987; 96: 282–8.

Raised intracranial pressure. Glycerol has been given intravenously or orally for its osmotic diuretic effect to reduce cerebral oedema and hence decrease the intracranial pressure (p. 1271.3). It is also reported to be able to increase blood flow to areas of brain ischaemia. It has been used in a variety of clinical conditions[1] including cerebral infarction or stroke,[2] Reye's syndrome,[3] and meningitis.[4,5] It has been postulated[5] that glycerol's beneficial action in preventing the neurological sequelae in bacterial meningitis is due to its effects in increasing cerebral plasma osmolality, which reduces cerebral oedema and enhances cerebral circulation by reducing the excretion of cerebrospinal fluid, and that this may be more important than the decrease in intracranial pressure induced by osmotic diuresis. Glycerol has been reported to be ineffective in hepatic coma.[6] Some patients have had serious adverse effects including haemolysis, haemoglobinuria, and renal failure.[7,8]

1. Frank MSB, *et al.* Glycerol: a review of its pharmacology, pharmacokinetics, adverse reactions, and clinical use. *Pharmacotherapy* 1981; 1: 147–60.
2. Righetti E, *et al.* Glycerol for acute stroke. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 23/05/06).
3. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; 29: 782–7.
4. Kilpi T, *et al.* Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J* 1995; 14: 270–8.
5. Peltola H, *et al.* Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2007; 45: 1277–86.
6. Record CO, *et al.* Glycerol therapy for cerebral oedema complicating fulminant hepatic failure. *BMJ* 1975; ii: 540.
7. Hägnevik K, *et al.* Glycerol-induced haemolysis with haemoglobinuria and acute renal failure: report of three cases. *Lancet* 1974; i: 75–7.
8. Welch KMA, *et al.* Glycerol-induced haemolysis. *Lancet* 1974; i: 416–17.

Skin disorders. The use of glycerol in skin disorders has been reviewed.[1] The hydrophilic hydroxyl groups present in glycerol are responsible for its properties of hygroscopicity and water solubility, and endogenous glycerol (synthesised in the pilosebaceous unit) has been shown to play a role in skin homoeostasis and maintenance of the function of the epidermal barrier. Glycerol has a long history of use in topical skin formulations and is widely used as an emollient and to improve skin smoothness. A greater understanding of the biological and biophysical effects of glycerol on the skin suggests additional properties of glycerol as a keratolytic, anti-irritant, skin barrier, or UV protectant. It is also reported to have antimicrobial properties, and to promote wound healing.

1. Fluhr JW, *et al.* Glycerol and the skin: holistic approach to its origin and functions. *Br J Dermatol* 2008; 159: 23–34.

Trigeminal neuralgia. Selective destruction of pain-bearing nerves is reserved for patients who do not respond to conventional drug therapy for trigeminal neuralgia (p. 11.2). This may be achieved by the instillation of glycerol among the trigeminal rootlets (percutaneous retrogasserian glycerol rhizolysis).[1-5] The efficacy and safety of this procedure have been debated,[1,4] but some centres report

good long-term results in the majority of patients.[5] It has been suggested that variations in viscosity and osmolality may influence results.[2]

1. Sweet WH. The treatment of trigeminal neuralgia (tic douloureux). *N Engl J Med* 1986; 315: 174–7.
2. Waltz TA, Copeland BR. Treatment of trigeminal neuralgia. *N Engl J Med* 1987; 316: 693.
3. Young RF. Glycerol rhizotysis for treatment of trigeminal neuralgia. *J Neurosurg* 1988; 69: 39–45.
4. Burchiel KJ. Percutaneous retrogasserian glycerol rhizolysis in the management of trigeminal neuralgia. *J Neurosurg* 1988; 69: 361–6.
5. Jho H-D, Lunsford LD. Percutaneous retrogasserian glycerol rhizotomy: current technique and results. *Neurosurg Clin N Am* 1997; 8: 63–74.

Adverse Effects and Precautions

The adverse effects of glycerol are mainly due to its dehydrating action.

When taken orally glycerol may cause headache, nausea, and vomiting; diarrhoea, thirst, dizziness, and mental confusion may occur less frequently. Cardiac arrhythmias have been reported.

Glycerol increases plasma osmolality resulting in the withdrawal of water from the extravascular spaces. The consequent expansion of extracellular fluid, especially if sudden, can lead to circulatory overload, pulmonary oedema, and heart failure; glycerol must therefore be used with caution in patients at risk, such as those with hypervolaemia, cardiac failure, or renal disease. Severe dehydration can occur and glycerol should be used cautiously in dehydrated patients. Patients with diabetes mellitus may additionally develop hyperglycaemia and glycosuria after metabolism of glycerol. Nonketotic hyperosmolar hyperglycaemic coma is rare, but fatalities have been reported.

Haemolysis, haemoglobinuria, and acute renal failure have also been associated with glycerol when given intravenously (see Raised Intracranial Pressure, p. 2517.3).

Glycerol can cause irritation when given topically or rectally. A local anaesthetic may be used before application of glycerol to the cornea to reduce the likelihood of a painful response.

For incompatibilities with glycerol, including the risk of explosive mixtures, see p. 2517.2.

Effects on the cardiovascular system. A 73-year-old man, free of cardiac complaints but who had previously had an acute myocardial infarction, developed severe pulmonary oedema after use of glycerol orally for elevated intra-ocular pressure.[1] The necessity for detailed cardiac evaluation before the use of oral glycerol was emphasised.

1. Almog Y, *et al.* Pulmonary edema as a complication of oral glycerol administration. *Ann Ophthalmol* 1986; 18: 38–9.

Effects on the ears. A 56-year-old man given 100 mL of glycerol and 100 mL of sodium chloride 0.9% as part of a test for Ménière's disease developed temporary hearing loss in the non-involved ear. Two previous reports of deterioration in hearing associated with the glycerol test were reviewed by the author.[1]

1. Mattox DE, Goode RL. Temporary loss of hearing after a glycerin test. *Arch Otolaryngol* 1978; 104: 359–61.

Effects on the eyes. Caution in applying glycerol to the cornea has been recommended. Studies in *animals*[1] and in man[2] have indicated that the topical application of glycerol to the eye can damage the endothelial cells of the cornea.

1. Sherrard ES. The corneal endothelium in vivo: its response to mild trauma. *Exp Eye Res* 1976; 22: 347–57.
2. Goldberg MH, *et al.* The effects of topically applied glycerin on the human corneal endothelium. *Cornea* 1982; 1: 39–44.

Hyperosmolar nonketotic coma. Hyperosmolar nonketotic coma has been associated with the oral use of glycerol[1] and deaths have occurred.[2] The most susceptible patients are maturity-onset elderly diabetics with acute or chronic disease predisposing to fluid deprivation, and in these patients oral glycerol may be best avoided.[1] If glycerol is used in patients with predisposing conditions, adequate measures should be taken to recognise the development of hyperosmolar nonketotic hyperglycaemia and prevent dehydration.[1,2]

1. Oakley DE, Ellis PP. Glycerol and hyperosmolar nonketotic coma. *Am J Ophthalmol* 1976; 81: 469–72.
2. Sears ES. Nonketotic hyperosmolar hyperglycemia during glycerol therapy for cerebral edema. *Neurology* 1976; 26: 89–94.

Overdosage. References.

1. Singh R, *et al.* Reversible neurologic manifestations after glycerol: a short report. *Neurol India* 2001; 49: 320–1.
2. Bingel U, *et al.* Acute encephalopathy due to glycerol over-consumption. *J Neurol* 2006; 253: 125–6.
3. Andresen H, *et al.* Severe glycerol intoxication after Menière's disease diagnostic—case report and overview of kinetic data. *Clin Toxicol* 2009; 47: 312–16.

Pharmacokinetics

Glycerol is readily absorbed from the gastrointestinal tract and undergoes extensive metabolism, mainly in the liver; it may be used in the synthesis of lipids, metabolised to glucose or glycogen, or oxidised to carbon dioxide and water. It may also be excreted in the urine unchanged.

References.

1. Nahata MC, *et al.* Variations in glycerol kinetics in Reye's syndrome. *Clin Pharmacol Ther* 1981; 29: 782–7.
2. Heinemeyer G. Clinical pharmacokinetic considerations in the treatment of increased intracranial pressure. *Clin Pharmacokinet* 1987; 13: 1–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Refenax Lagrimas; Vixorfit; *Austral.*: Bausch & Lomb Computer Eye Drops†; Becoderm†; *Braz.*: Endura; Glicel; *Canad.*: Bandi†; Synovisol; Universal Brand Enema†; *Chile*: Fleet Babylax; *China*: Xin Long (信龙); *Fin.*: Miniderm; *Fr.*: Bebegel; Cristal; *Ger.*: Babylax; Glycerosteril; Glycilax; Milax; Nene-Lax; Otodolor Soft; *Gr.*: Babylax; Glicerolo microclismi; Gly Care; Microclismata†; Pikefi; *Hong Kong*: Computer Eye Drops; Fleet Babylax†; Glyceol; Wet Stuff; *India*: Hidrate; *Irl.*: Babylax; *Ital.*: Bonlax; Verolax; Zetalax; *Jpn*: Glyceol; *Malaysia*: Egozite Protective Baby Lotion†; Fleet Babylax†; ZenCare; *Mex.*: Estrin; Fleet Adulto†; Fleet Infantil†; Fleet Pedialax†; Micronovag; Neutrobar; PC; Supositorios Senosiain; *Philipp.*: Babylax; Computer Eye Drops; Novas; United Home Glydolax; *Port.*: Bebegel; Dolorecto†; Glycelax; Rectiole; Verolax; *Rus.*: Glycelax (Глицелакс); *S.Afr.*: Regard†; *Singapore*: Fleet Babylax; Optive; *Spain*: Adulax; Comosup; Dulcoenema; Gely†; Glicerotens; Kanova; Normovagil; Paidolax; Supogliz†; Verolax; Vitrosups†; *Switz.*: Bulboid; Practomil; *Thai.*: Glyceol; Glycerosteril; *UAE*: Laxolyne; *UK*: Benylin Childrens Apple Flavour Cough Syrup; Benylin Tickly Coughs; Boots Constipation Relief; Boots Cough Syrup 3 Months Plus; CalCough Children's Soothing Syrup; CalCough Infant Syrup; CalCough Tickly†; Neutrogena Norwegian Formula Dermatological Cream; Nirolex Dry Cough; Senokot Direct Relief; Tixylix; *Ukr.*: Adulax (Адюлакс); Peidolax (Пейдолакс); *USA*: Colace Infant/Child; Eye-Lube-A; Fleet Babylax; Listermint Arctic Mint Mouthwash; Osmoglyn†; Pedia-Lax; Sani-Supp; *Venez.*: Fleet Babylax.

Multi-ingredient Preparations. *Arg.*: Aftersun; Cutidermin Crema Antibacterial†; Endura; Irix Lagrimas; Keracnyl; Micronema; Optive; Sincerum Dry; Tears Naturale Forte; Tears Naturale†; Ureadin Facial; Visine Lagrimas; *Austral.*: Anusol†; EgoPsoryl TA; Gentlees; Hamilton Dry Skin; Hamilton Skin Active Urederm Cream; Magnoplasm; Micolette; Optive; QV Flare Up; SM-33; Soothe'n Heal†; *Belg.*: Aloplastine†; Laxavit; *Braz.*: Dermamina; Optive; Trisorb; *Canad.*: Agarol Plain; Auralgan; Bausch & Lomb Moisture Eyes; Clear Eyes for Dry Eyes Plus Redness Relief; Clear Eyes for Dry Eyes; Epi-Lyt; Refresh Ultra; Tears Naturale Forte; Tucks†; *Chile*: Acnoxyl Jabon Liquido†; Agarol†; Cicapost; Ictyane; Keracnyl; Nasivin; Optive; Tears Visine†; Ureadin Rx DB; Ureadin Rx RD; *China*: Bu Rui De (布瑞得); Ganruining (甘瑞宁); Tears Naturale Forte (新泪然); *Denm.*: Glyoktyl; Pectyl; *Fr.*: Aloplastine; Derm'Intim; Dexeryl; Ictyane HD; Ictyane; Kertyol PSO; Kertyol-S†; Lubri-Mucal; Naturophta Macula; Pharyndol; Pharyndol; PSO†; Rectopanbiline; Saugella Antiseptic; Saugella Dermoliquide; Scleremo; Taido; Topicrem†; Totephan†; Urgo Cicatrices; *Ger.*: Dexeryl; GeloBacin; InfectoGripp; Lacrisic; Lubricano; Norgalax Miniklistier†; Norgalax Rektalgel; Optive; Otodolor; Silence; Zinksalbe; *Hong Kong*: Acnederm Wash; Acnederm; Asonor; Baby Cough with Antihistamine†; Ego Skin Cream; Egopsoryl TA; Gly Thymol; Moisture Eyes; Optive; Tears Naturale Forte; Visine for Contacts†; *Hung.*: Strand; *India*: Alv; Clenora; Clenorush; Coldtaur; Dentra; Dermamoist; Dew Derm; Diafoot; Dordent; Glyvin; Glyvine-S; Icee; Kratol; Mannigyl; Mengy; Neotomic; Neurotol; Novaglow; Otogesic; *Indon.*: Isotic Tearin; Laxadine; *Irl.*: Lemsip Dry Cough; Micolette; *Israel*: Claritone; DryEars; Kamil Blue; Microlet; Optive; *Ital.*: Cue Soluzione Otologica; Dropyal; Evasen Dischetti; Evasen Liquido; Glicerolax; Lipimix; Microclismi Marco Viti†; Naturalass; Novilax; Rinogutt Atlantic; Salviette H; Solecin†; *Malaysia*: AcneCare; Acnederm Foaming Wash; Aqua Care; Cationorm; Ego Skin Cream; Lanakeloid-E; Panoff; pH Care; Prelactic; *Mex.*: Moisture Eyes; Nasalub; Nutrasorb; Optive; ProcalAmine; Varicyl; *NZ*: Acnederm Foaming Wash†; Auralgan; Ego Skin Cream; Rosken Skin Repair; Silic; *Philipp.*: BioSil†; Lactaderm†; Medisnore; Moisture Eyes; Optive; pH Care; Visine Refresh; *Pol.*: Rektiolax; Unibasis; *Port.*: Cicapost; Dagragel; Hidratante VG; Nutraisdin; Ureadin Facial; Ureadin Manos; *Rus.*: Proposol-N (Пропосол-Н); *S.Afr.*: Auralyt†; Caloplast†; *Singapore*: Acnederm Foaming Wash; Acnederm; Arkopharma Propolis Spray; Bio-Taches Masquet†; Ego Skin Cream; Endura; Lanakeloid-E; Minica S; Panoff; pH Care Intimate Wash; Silence; Snoreeze; Topicrem; Tropex; *Spain*: Enofosforina Vigor†; *Switz.*: Dexeryl; Lacrycon; Neo-Decongestine; Optive; Realderm; Silence†; Silence; *Thai.*: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; Endura; Optive; *Turk.*: Gleitgelen; Kalmosan; Kansilak; Libalaks; Sabalaks; Snoreless; *UK*: Allens Junior Cough; Asonor; Beehive Balsam; Earex Plus†; Feminesse; Glycerdex; Honey & Molasses; Imuderm†; Jackson's Lemon Linctus; Jackson's Troublesome Coughs; Lemsip Cough & Cold Dry Cough; Lockets Medicated Linctus; Lockets; Meltus Honey & Lemon; Micolette; Murine Dry & Tired Eyes; Optive; Relaxit; Swim-Ear; *Ukr.*: Optive (Оптиве); *USA*: Allergen; Astroglide; Auralgan; Aurax; Cetaklenz; Clearasil Antibacterial; Dri/Ear; Entertainer's Secret; Epi-Lyt; Episil; Formulation R; Hemorid For Women; Maxilube; Mimyx†; Moisture Drops; MuGard; N'ice; Neosalus; Neotic†; Ocean Nasal Moisturizer; Otic Edge†; Otozin; Preparation H; Refresh Dry Eye Therapy; Summer's Eve Anti-Itch; Surgel; Therevac Plus; Therevac SB; Tonsiline; Trimo-San; Tucks; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief.

Pharmacopoeial Preparations

BP 2014: Glycerol Eye Drops; Glycerol Suppositories; Phenol and Glycerol Injection;

USP 36: Antipyrine and Benzocaine Otic Solution; Calamine Topical Suspension; Glycerin Ophthalmic Solution; Glycerin Oral Solution; Glycerin Suppositories.

Glycerol Phenylbutyrate *(USAN, pINN)*

Fenilbutirato de Glicerol; Glyceroli Phenylbutyras; Glyceryl Tri (4-Phenylbutyrate); HPN-100; Phénylbutyrate de Glycérol; Глицеролфенилбутират.

Propane-1,2,3-triyl tris(4-phenylbutanoate).

$C_{33}H_{38}O_6$=530.7

CAS — 611168-24-2.

ATC — A16AX09.

ATC Vet — QA16AX09.

UNII — ZH6F1VCV7B.

Sodium Phenylbutyrate *(BAN, USAN)*

Fenilbutirato de sodio; Natrii phenylbutyras; Natriumfenylbutyrat; Natriumfenylbutyraatti; Natriumphenylbutyrat; Sodium, phénylbutyrate de; Sodyum Fenilbutirat; Фенилбутират Натрия.

Sodium 4-Phenylbutyrate.

$C_{10}H_{11}NaO_2$=186.2

CAS — 1716-12-7.

ATC — A16AX03.

ATC Vet — QA16AX03.

UNII — NT6K61736T.

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

Ph. Eur. 8: (Sodium Phenylbutyrate). A white or yellowish-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5.

Uses and Administration

Sodium phenylbutyrate is a prodrug for sodium phenylacetate (p. 2619.2) and glycerol phenylbutyrate is a prodrug for phenylbutyrate. They provide alternative metabolic routes for the excretion of waste nitrogen and are used as adjunctive therapy in the chronic treatment of hyperammonaemia (p. 2049.3) in patients with urea cycle disorders.

Both are given orally in equally divided doses with meals. The daily dose is adjusted according to protein tolerance and the required dietary protein intake for growth and development. In adolescents and adults the usual total daily dose of sodium phenylbutyrate is 9.9 to 13.0 g/m² to a maximum of 20 g daily. Glycerol phenylbutyrate is a liquid containing 1.1 g/mL, and is given in a total daily dose ranging from 4.5 to 11.2 mL/m² (5 to 12.4 g/m²), to a maximum daily dose of 17.5 mL (about 19 g). To provide the same dose of phenylbutyric acid when converting between the two:

$$\text{glycerol phenylbutyrate (mL)} = \text{sodium phenylbutyrate (g)} \times 0.86$$

For doses used in children, see p. 2519.1.

Sodium phenylbutyrate is also under investigation for the treatment of some sickle-cell disorders (p. 1123.2) and for use as a potential differentiation-inducing agent in malignant glioma and acute myeloid leukaemia. Sodium phenylbutyrate is also under investigation for spinal muscular atrophy, which is caused by homozygous absence of the SMN1 gene, after reports that it significantly increased SMN transcript expression in both fibroblast cultures and leucocytes from these patients.

References.

1. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; 138 (suppl 1): S46–S55. Correction. *Ibid.* 2002; 140: 490.
2. Mercuri E, *et al.* Randomized, double-blind, placebo-controlled trial of phenylbutyrate in spinal muscular atrophy. *Neurology* 2007; 68: 51–5.
3. Caruthers RL, Johnson CE. Stability of extemporaneously prepared sodium phenylbutyrate oral suspensions. *Am J Health-Syst Pharm* 2007; 64: 1513–15.
4. Lee B, *et al.* Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. *Mol Genet Metab* 2010; 100: 221–8.
5. Lichter-Konecki U, *et al.* Ammonia control in children with urea cycle disorders (UCDs); phase 2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate. *Mol Genet Metab* 2011; 103: 323–9.
6. Iannitti T, Palmieri B. Clinical and experimental applications of sodium phenylbutyrate. *Drugs R D* 2011; 11: 227–49.

Administration in children. Sodium phenylbutyrate and glycerol phenylbutyrate are used as adjunctive therapy in the chronic treatment of hyperammonaemia in infants and children with urea cycle disorders. They are given orally in equally divided doses with each meal or feed. The daily dose is adjusted according to protein tolerance and the required dietary protein intake for growth and development.

The usual total daily dose of sodium phenylbutyrate for patients weighing under 20 kg is 450 to 600 mg/kg. Those weighing 20 kg or more may be given the adult dose (see p. 2518.3). Alternatively, the *BNFC* suggests a dose of 75 to 150 mg/kg given 3 or 4 times daily for neonates and children up to 18 years of age.

Glycerol phenylbutyrate may be used in children aged 2 years and older; doses are calculated using the same regimen as that used in adults. There is limited data on the safety and efficacy of its use in children aged 2 months to 2 years, and it is contra-indicated in those less than 2 months old.

For the treatment of acute hyperammonaemia due to urea cycle disorders in neonates and children up to 18 years of age, the *BNFC* includes an unlicensed dose of sodium phenylbutyrate given by continuous intravenous infusion. An initial dose of 250 mg/kg is given over 90 minutes, followed by 20 mg/kg per hour adjusted according to response.

Adverse Effects and Precautions

Adverse effects of sodium phenylbutyrate include gastrointestinal disturbances, decreased appetite, taste disturbance, rashes, dizziness, headache, fatigue, depression, oedema, and weight gain. Abnormal body odour, probably caused by the metabolite phenylacetate, is commonly reported. Amenorrhoea or irregular menstruation is very common. Reported haematological disturbances include anaemia, thrombocytopenia, leucopenia, thrombocytosis, and leucocytosis.

Electrolyte disturbances, metabolic acidosis, alkalosis, and renal tubular acidosis are common. Increases in hepatic enzymes, bilirubin, and uric acid can occur. Sodium phenylbutyrate should be used with caution, if at all, in patients with congestive heart failure or severe renal impairment because of its high sodium content (see Sodium Content, below). It should also be used with caution in patients with milder renal impairment, hepatic impairment, or inborn errors of beta oxidation.

Adverse effects of glycerol phenylbutyrate are similar to those of sodium phenylbutyrate, although diarrhoea and flatulence may be more common. Glycerol phenylbutyrate is contra-indicated in children younger than 2 months old; their immature pancreatic exocrine function may not produce sufficient lipases for intestinal hydrolysis to release phenylbutyrate. Similarly, the efficacy of glycerol phenylbutyrate may be reduced in patients with pancreatic insufficiency or conditions of intestinal malabsorption.

Sodium content. Each g of sodium phenylbutyrate contains about 5.4 mmol of sodium.

Interactions

Probenecid may inhibit the renal excretion of the metabolites of sodium phenylbutyrate and glycerol phenylbutyrate.

Pharmacokinetics

Sodium phenylbutyrate is rapidly absorbed from the gastrointestinal tract and oxidised to phenylacetate, which undergoes glutamine conjugation via acetylation in the liver and kidney to form phenylacetylglutamine. Peak plasma concentrations of phenylacetate and phenylacetylglutamine occur after about 3 to 4 hours. About 80 to 100% of a dose of sodium phenylbutyrate is renally excreted as phenylacetylglutamine within 24 hours, providing an alternative route for nitrogen excretion. Phenylacetate also undergoes some hydrolysis by esterases in the blood and liver.

After oral administration, glycerol phenylbutyrate is hydrolysed by pancreatic lipases in the gastrointestinal tract to release phenylbutyrate, which is rapidly absorbed and metabolised as described above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Ammonaps; *Belg.*: Ammonaps; *Cz.*: Ammonaps; *Denm.*: Ammonaps; *Fr.*: Ammonaps; *Ger.*: Ammonaps; *Gr.*: Ambutyrate; *Irl.*: Ammonaps; *Ital.*: Ammonaps; *Jpn*: Buphenyl; *Mex.*: Pegabiral; *Neth.*: Ammonaps; *Norw.*: Ammonaps; *Pol.*: Ammonaps; *Port.*: Ammonaps; *Spain*: Ammonaps; *Swed.*: Ammonaps; *UK*: Ammonaps; *USA*: Buphenyl; Ravicti.

Pharmacopoeial Preparations
USP 36: Sodium Phenylbutyrate Oral Suspension.

Glycerophosphoric Acid

Glicerofosfórico, ácido; Glycerylphosphoric Acid; Monoglycerylphosphoric Acid; Глицерофосфорная Кислота.
$C_3H_9O_6P$=172.1.
CAS — 27082-31-1; 57-03-4 (α-glycerophosphoric acid); 17181-54-3 (β-glycerophosphoric acid); 5746-57-6 (L-α-glycerophosphoric acid); 1509-81-5 (DL-α-glycerophosphoric acid).
UNII — MG976Z29OM.

Sodium Glycerophosphate *(USAN)*

Glycerofosforečnan sodný; Natrii glycerophosphas; Natrio glicerofosfatas; Natrium Glycerophosphoricum; Nátriumglicerofoszfát; Natriumglycerofosfat; Natriumglyserofosfaatti hydratoitu; Sodium, glycérophosphate de; Sodium Glycerylphosphate; Глицерофосфат Натрия.
$C_3H_9O_6P.2Na.xH_2O$=218.1 (anhydrous).
CAS — 1334-74-3 (anhydrous sodium glycerophosphate); 1555-56-2 (anhydrous α-sodium glycerophosphate); 819-83-0 (anhydrous β-sodium glycerophosphate); 55073-41-1 (sodium glycerophosphate).
ATC — B05XA14.
ATC Vet — QB05XA14.
UNII — YP1H63LJ2K.

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

Ph. Eur. 8: (Sodium Glycerophosphate, Hydrated). A mixture of variable proportions of sodium (2*RS*)-2,3-dihydroxypropyl phosphate and sodium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. It may contain various amounts of other glycerophosphate esters. The degree of hydration is 4 to 6. A white or almost white, crystalline powder or crystals. Freely soluble in water; practically insoluble in alcohol and in acetone.

Profile

Glycerophosphoric acid and various glycerophosphates have been used in tonics. They were once considered as a suitable means of providing phosphorus. Calcium and magnesium glycerophosphates (see p. 1783.3 and p. 1787.2, respectively) may be considered as a source of calcium or magnesium.

Reference to the use of sodium glycerophosphate as a source of phosphorus in infant parenteral nutrition.[1]

1. Costello I, *et al.* Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. *Arch Dis Child* 1995; 73: F44–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium glycerophosphate 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 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Glycophos (格利福斯); *Denm.*: Glycophos; *Fin.*: Glycophos; *Gr.*: Glycophos; *Hong Kong*: Glycophos; *Malaysia*: Glycophos†; *Neth.*: Glycophos; *NZ*: Glycophos; *Pol.*: Glycophos; *Port.*: Glycophos; *Spain*: Glycophos; *Swed.*: Glycophos; *Switz.*: Glycophos; *Thai.*: Glycophos; *Turk.*: Glycophose; *UK*: Glycophos.

Multi-ingredient Preparations. *Braz.*: Ferrotrat B12 Plus; *Canad.*: Hemarexin†; *Chile*: Paralymphine; *China*: Diweijia (迪维佳); *Fr.*: Biotone; Phosphore Alko; Stimuplexe†; Verrulyse-Methionine; *India*: Deferon; Neurophosphates-Iron; *Indon.*: Tonikum Bode; *Irl.*: Metatone; *Israel*: Babyzim; *Ital.*: Glicero-Valerovit; Neurol; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); *Spain*: Enofosforina Vigor†; *UK*: Metatone.

Glycogen

Animal Starch; Liver Starch.
$(C_6H_{10}O_5)_n$.
CAS — 9005-79-2.
UNII — 309GSC92U1.

Profile

Glycogen is a polysaccharide composed of glucose subunits and is the main storage form for carbohydrate in animals. It has been used with lactic acid in preparations for vaginal disorders since it has been suggested that vaginal bacteria may utilise glycogen to produce an acidic environment, but this is not established.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Geliofil; *Ger.*: Gelifend; *Israel*: Femina Lactal; *Ital.*: Geliofil; *Singapore*: Luvena Prebiotic; *UK*: Balance Activ RX; *Ukr.*: Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос).

Homoeopathic Preparations. *UK*: Pragador.

Glycopyrronium Bromide *(BAN, rINN)*

AHR-504; Bromuro de glicopirronio; Glicopirronio; bromuro de; Glikopironyum Bromür; Glycopyrrolate (USAN); Glycopyrronii Bromidum; Glycopyrronium, bromure de; Glykopyrroniumbromid; Glykopyrroniumbromidi; NVA-237; Гликопирония бромид.
3-(α-Cyclopentylmandeloyloxy)-1,1-dimethylpyrrolidinium bromide.
$C_{19}H_{28}BrNO_3$=398.3.
CAS — 596-51-0; 51186-83-5.
ATC — A03AB02; R03BB06.
ATC Vet — QA03AB02; QR03BB06.
UNII — V92SO9WP2I.

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

Ph. Eur. 8: (Glycopyrronium Bromide). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane.

USP 36: (Glycopyrrolate). A white, odourless, crystalline powder. Soluble 1 in 4.2 of water, 1 in 30 of alcohol, 1 in 260 of chloroform, and 1 in 35 000 of ether. Store in airtight containers.

Incompatibility. Glycopyrronium bromide is incompatible with alkalis.

Stability. Investigation of the compatibility of glycopyrronium bromide with infusion solutions and additives showed that the stability of glycopyrronium bromide is questionable above a pH of 6, owing to ester hydrolysis.[1]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; 36: 508–10. Correction. *ibid.*: 745.

Uses and Administration

Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p. 1312.1). After intramuscular doses, onset of effects is within 15 to 30 minutes; vagal blocking effects last for 2 to 3 hours and antisialagogue effects persist for up to 7 hours. After intravenous doses, onset of actions occurs within 1 minute.

Glycopyrronium bromide is used similarly to atropine in anaesthetic practice (below). It has also been used in the iontophoretic treatment of hyperhidrosis (p. 2520.1) and as an adjunct in the treatment of peptic ulcer disease (p. 2520.1). It is also used for the treatment of chronic severe drooling in children (p. 2520.1) and as a bronchodilator in the maintenance treatment of chronic obstructive pulmonary disease (p. 2520.1).

Administration in children. Doses of glycopyrronium bromide in children are given below under Anaesthesia (below), Drooling (p. 2520.1), and Palliative Care (p. 2520.1).

Anaesthesia. Glycopyrronium bromide is given as a premedicant before general anaesthesia (see under Atropine, p. 1311.1) to diminish the risk of vagal inhibition of the heart and to reduce salivary and bronchial secretions. It is given in doses of 200 to 400 micrograms intravenously or intramuscularly before the induction of anaesthesia; alternatively, it may be given in a dose of 4 to 5 micrograms/kg to a maximum of 400 micrograms. If necessary, similar doses may be given intravenously during the operation and repeated if required. A suggested dosage for premedication in neonates is 5 micrograms/kg given intravenously or intramuscularly; doses in children aged 1 month and over are 4 to 8 micrograms/kg up to a maximum of 200 micrograms.

Glycopyrronium bromide is given before or with anticholinesterases to counteract their muscarinic effects when they are used to reverse the effects of competitive muscle relaxants (see Neostigmine, p. 687.2). The dose is glycopyrronium bromide 200 micrograms intravenously per 1 mg of neostigmine (or per 5 mg of pyridostigmine); alternatively, it may be given in a dose of 10 to 15 micrograms/kg intravenously with neostigmine 50 micrograms/kg. A suggested dosage for neonates and children is 10 micrograms/kg intravenously with neostigmine 50 micrograms/kg up to a maximum of glycopyrronium bromide 500 micrograms. Glycopyrronium bromide can be given mixed in the same syringe with the

anticholinesterase, and it has been suggested that greater cardiovascular stability results from use in this way.

Drooling. Glycopyrronium bromide is given orally to reduce chronic severe drooling in children aged 3 to 16 years with neurologic conditions such as cerebral palsy. The starting dose is 20 micrograms/kg 3 times daily increased in increments of 20 micrograms/kg every 5 to 7 days according to response and adverse effects over a 4-week titration period. The maximum recommended dose is 100 micrograms/kg 3 times daily, but not to exceed 1.5 to 3 mg per dose based on weight. The dose should be taken at least 1 hour before, or 2 hours after, meals.

Gastrointestinal disorders. Antimuscarinics, including glycopyrronium bromide, have a limited role as antispasmodics (see p. 1803.3), and have been used as adjuncts in the treatment of peptic ulcer disease (see p. 1813.2).

As an adjunct in the treatment of peptic ulcer disease the usual initial oral dose of glycopyrronium bromide has been 3 to 6 mg daily in divided doses adjusted according to response to a maximum of 8 mg daily; a maintenance dose of 1 mg twice daily is often adequate. Doses of 100 to 200 micrograms have been given by intramuscular or intravenous injection.

Hyperhidrosis. Adverse effects generally preclude oral use of antimuscarinics for the management of hyperhidrosis (p. 1685.1), but glycopyrronium, has been applied topically as an alternative to aluminium salts.

In studies involving 22 patients with the Frey syndrome (localised flushing and sweating on eating) glycopyrronium bromide as 1 and 2% cream or roll-on solution gave good control of symptoms;[1] patients tended to prefer the roll-on lotion as it was easier to apply. Topical hyoscine as 0.25, 1, or 3% solution or cream also controlled sweating, but was associated with a much higher incidence of adverse effects. Reports of adverse effects produced by systemic absorption of topical glycopyrronium bromide used for hyperhidrosis include urinary retention[2] and dilated pupils;[3] ocular adverse effects may also be produced following peri-ocular contamination.[4] Patients with diabetic gustatory sweating have also noted a reduction in the frequency and severity of episodes after applying glycopyrronium 0.5% cream.[5]

Glycopyrronium bromide has also been used as a 0.05% solution in the iontophoretic treatment of hyperhidrosis.

Oral glycopyrronium bromide has been tried successfully in a patient with diabetic gustatory sweating.[6] Oral use was also shown to be of benefit in a retrospective analysis[7] of patients who had been treated for idiopathic hyperhidrosis over the previous 4 years. Out of 19 patients evaluated, only 4 stopped treatment due to lack of response; however, a further 5 stopped treatment because of intolerable adverse effects, mainly dry mouth.

1. Hays LL, *et al.* The Frey syndrome: a simple, effective treatment. *Otolaryngol Head Neck Surg* 1982; 90: 419–25.
2. Madan V, Beck MH. Urinary retention caused by topical glycopyrrolate for hyperhidrosis. *Br J Dermatol* 2006; 155: 634–5.
3. Panting KJ, *et al.* Dilated pupils caused by topical glycopyrrolate for hyperhidrosis. *Br J Dermatol* 2008; 158: 187–8.
4. Izadi S, *et al.* Mydriasis and accommodative failure from exposure to topical glycopyrrolate used in hyperhidrosis. *J Neuroophthalmol* 2006; 26: 232–3.
5. Shaw JE, *et al.* A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997; 40: 299–301.
6. Edick CM. Oral glycopyrrolate for the treatment of diabetic gustatory sweating. *Ann Pharmacother* 2005; 39: 1760.
7. Bajaj V, Langtry JAA. Use of oral glycopyrronium bromide in hyperhidrosis. *Br J Dermatol* 2007; 157: 118–21.

Palliative care. Glycopyrronium bromide is used in palliative care as an alternative to hyoscine to reduce excessive respiratory secretions. A dose of 200 micrograms may be given subcutaneously or intramuscularly every 4 hours to adults. Alternatively, a dose of 0.6 to 1.2 mg may be given by continuous subcutaneous infusion over 24 hours.

For the control of upper airways secretion and hypersalivation in children aged 1 month and over, the *BNFC* recommends a dose of 40 to 100 micrograms/kg given orally 3 or 4 times daily adjusted according to response up to a maximum of 2 mg. Alternatively, children aged 1 month to 12 years may be given glycopyrronium bromide by subcutaneous infusion in a dose of 12 to 40 micrograms/kg over 24 hours up to a maximum of 1.2 mg; children over 12 years of age may receive the same dose by continuous subcutaneous infusion as for adults (see above).

References.
1. Kintzel PE, *et al.* Anticholinergic medications for managing noisy respirations in adult hospice patients. *Am J Health-Syst Pharm* 2009; 66: 458–64.

Respiratory-tract disorders. Antimuscarinics have potent bronchodilatory activity and some, such as ipratropium (p. 1211.3), may be used in the management of reversible airways obstruction. Glycopyrronium bromide is also used in the maintenance treatment of chronic obstructive pulmonary disease, although it is not suitable for the initial treatment of acute bronchospasm. It can be given as inhalation powder in capsules containing 63 micrograms of glycopyrronium bromide, equivalent to 50 micrograms of glycopyrronium, and supplying 44 micrograms of glycopyrronium from the mouthpiece of the inhaler device. The contents of one capsule are inhaled once daily, at the same time each day.

References.
1. Schroeckenstein DC, *et al.* Twelve-hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988; 82: 115–19.
2. Gilman MJ, *et al.* Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990; 98: 1095–8.
3. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1995; 25: 470–3.
4. Buhl R, Banerji D. Profile of glycopyrronium for once-daily treatment of moderate-to-severe COPD. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 729–41.
5. Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 673–8.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glycopyrronium bromide 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)

Renal impairment. A comparison[1] of the pharmacokinetics of intravenous glycopyrronium in 11 uraemic and 7 control patients indicated that the renal elimination of glycopyrronium is considerably prolonged in patients with uraemia. The mean amount of a dose excreted in the urine within 3 hours of a dose was 0.7% in the uraemic patients and 50% in the control patients; 24-hour excretion was 7% and 65%, respectively. The authors concluded that repeated or large doses of glycopyrronium should be avoided or perhaps the drug should not be used in patients with uraemia.

1. Kirvelä M, *et al.* Pharmacokinetics of glycopyrronium in uraemic patients. *Br J Anaesth* 1993; 71: 437–9.

Interactions

As for Atropine Sulfate, p. 1312.3.

Pharmacokinetics

Glycopyrronium bromide is poorly absorbed from the gastrointestinal tract; about 10 to 25% is absorbed after an oral dose. Glycopyrronium bromide penetrates the blood-brain barrier only poorly. Glycopyrronium is excreted in bile and urine.

References.
1. Kaltiala E, *et al.* The fate of intravenous [^{3}H]glycopyrrolate in man. *J Pharm Pharmacol* 1974; 26: 352–4.
2. Ali-melkkilä TM, *et al.* Pharmacokinetics of IM glycopyrronium. *Br J Anaesth* 1990; 64: 667–9.
3. Rautakorpi P, *et al.* Pharmacokinetics of glycopyrrolate in children. *J Clin Anesth* 1994; 6: 217–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acpan; *Austral.*: Robinul; *Austria*: Robinul; *Belg.*: Robinul; *Denm.*: Robinul; Seebri; *Fin.*: Robinul; *Ger.*: Robinul; *Gr.*: Robinul; *India*: Glyco-P; Glyprolate; Lycolate; *Irl.*: Robinul; *Israel*: Seebri; *Jpn*: Seebri; *Neth.*: Enurev; Seebri; Tovanor; *Norw.*: Robinul; *NZ*: Robinul; *S.Afr.*: Robinul; *Spain*: Seebri; *Swed.*: Robinul; *UK*: Robinul†; Robinul; Seebri; *USA*: Cuvposa; Glycate; Robinul.

Multi-ingredient Preparations. *India*: Myo-Pyrolate.

Used as an adjunct inc. *Belg.*: Robinul-Neostigmine; *Denm.*: Robinul-Neostigmin; *Fin.*: Glycostigmin; Robinul-Neostigmin; *Norw.*: Robinul-Neostigmin; *Swed.*: Robinul-Neostigmin; *Switz.*: Robinul-Neostigmine; *UK*: Robinul-Neostigmine†.

Pharmacopoeial Preparations
BP 2014: Glycopyrronium Bromide Oral Solution;
USP 36: Glycopyrrolate Injection; Glycopyrrolate Tablets.

Glycyrrhizic Acid

Glycyrrhizin; Glycyrrhizinic Acid; Глицирризин; Глицирризиновая Кислота.
$C_{42}H_{62}O_{16}$=822.9
CAS — 1405-86-3.
ATC — A05BA08.
ATC Vet — QA05BA08.
UNII — 6FO62043WK.

Ammonium Glycyrrhizate

Ammonii Glycyrrhizas; Ammonium, glycyrrhizate d'; Ammonium Glycyrrhizinate; Ammónium-glicirrizát; Ammoniumglycyrrhizat; Ammoniumglykyrritsaatti; Amonio glicirrizatas; Amonium-glycyrrhizát; Glycyram; Monoammonium Glycyrrhizinate; Аммония Глицирризат.
$C_{42}H_{65}NO_{16}$=840.0
CAS — 53956-04-0.
UNII — 3VRD35U26C (ammonium glycyrrhizate); 1Z1Y4QY887 (anhydrous ammonium glycyrrhizate).

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

Ph. Eur. 8: (Ammonium Glycyrrhizate). A white or yellowish-white, hygroscopic powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. Store in airtight containers.

USNF 31: (Ammonium Glycyrrhizate). A white or yellowish-white, hygroscopic powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. It is a mixture of ammonium 18α- and 18β-glycyrrhizate (ammonium salt of (20β)-3β-[[2-*O*-(β-D-glucopyranosyluronic acid)-α-D-glucopyranosyluronic acid]oxy]-11-oxoolean-12-en-29-oic acid), and the 18β-isomer is the main component. It contains not less than 78.0% and not more than 102.0% of ammonium 18α- and 18β-glycyrrhizate, on the anhydrous basis. Store in airtight containers.

Dipotassium Glycyrrhizate

Potassium Glycyrrhizinate; Дикалия Глицериза.
$C_{42}H_{60}K_2O_{16}$=899.1
CAS — 68039-19-0 (potassium glycyrrhizate); 42294-03-1 (monopotassium glycyrrhizate); 68797-35-3 (dipotassium glycyrrhizate).
UNII — CA2Y0FE3FX.

Profile

Glycyrrhizic acid is a constituent of liquorice (p. 1853.2). The mild anti-inflammatory and mineralocorticoid properties of liquorice have been attributed to the presence of glycyrrhizic acid and its metabolite glycyrrhetinic acid (Enoxolone, p. 54.2).

Glycyrrhizic acid and its ammonium and potassium salts have been used in products promoted for the relief of coughs, viral infections, and gastrointestinal, liver, and skin disorders. Ammonium glycyrrhizate has also been used as a sweetener, flavour enhancer, and as an emulsifying and gel-forming agent in foodstuffs and cosmetics.

Other derivatives of glycyrrhizic acid include metoclopramide glycyrrhizinate (p. 1862.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Epigen; *China*: Ai Fu Bi (艾扶必); An Xin Fu Ning (安欣福宁); Dai Te (代特); Dan Wei (丹薇); Fu Luo Xin (福罗欣); Ming Ze (明择); Pu Gan Jing (普甘静); Tai Ka (泰卡); Tong Zhou (同洲); Wei Heng (维恒); WeiDing (卫丁); Xi Xin Sheng (喜心生); Xin Er Luo (信尔洛); Yong Bang (永邦); Yu Lu An (威卢安); Zhen Li Xin (振力辛); Zhi Gan Bao (知甘保); Zhuo Fang (卓方); *Indon.*: Glizigen; Neo-Minophagen C; *Jpn*: Glycyron; Neo-Minophagen C†; Neophagen C; *Mex.*: Epigen; *Rus.*: Epigen (Эпиген); Glycyram (Глицирам).

Multi-ingredient Preparations. *Chile*: Keracnyl Stop Bouton; *China*: BiFu (比孚); Bo Luo Ni (博罗尼); Gan Mu Shu (甘木舒); Gan Wei Xin (甘维欣); Gan You Lin (感佑林); Jun Qiang (君强); Kang Er Ning (康尔宁); LiWeiEr (里威尔); Neo-Minophagen C (美能); Neo-Minophagen C (美能); NuoHao (诺豪); Ruo Jing (若菁); Shu Kang Lin (抒康林); Tuo Di (妥迪); Wei Suan Su (卫算苏); Wei Yi Xing (卫伊兴); Xin Le Dun (新乐敦); Xin-Kang (昕康); Ye Xin (业欣); Yi Nuo Wei (依诺维); Yi Xin (易新); YouNiDi (尤尼迪); Yu Li Sen (宇立森); *Fr.*: Herpclair; Keracnyl stop bouton; Photerpes; *Hong Kong*: Scassh Trouch Lozenge; *Indon.*: Aviter; Viusid; *Ital.*: Biorag; Biothymus DS; Cue Soluzione Otologica; *Jpn*: Colgen Gargle†; Colgen Kowa for Rhinitis; *Port.*: Alkagin; Bexident; *Venez.*: Viusid.

GMDP

Glucosaminylmuramyl Dipeptide; ГМДП.
N-acetylglucosaminyl-β1-4-*N*-acetylmuramyl-alanyl-D-isoglutamine.
$C_{25}H_{43}N_5O_{15}$=653.6
CAS — 97590-38-0.

Profile

GMDP, a component of bacterial cell walls, is reported to have immunomodulator properties and is used in many

diseases stated to be associated with secondary immunodeficiency.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Licopid (Ликопид); *Ukr.*: Likopid (Ликопид).

Gold

Aurum; E175; Or; Oro; Золото.
Au=196.966569.
CAS — 7440-57-5.
UNII — 79Y1949PYO (gold); 7XM25QYI14 (gold ion).

Profile

Gold is a bright-yellow, malleable, and ductile metal; the finely divided powder may be black, ruby, or purple. The main use of metallic gold in healthcare is now in dentistry. Gold may also be used as a colouring agent for some foodstuffs. In the treatment of rheumatoid arthritis, gold is used in the form of compounds such as auranofin (p. 27.3), aurothioglucose (p. 28.2), and sodium aurothiomalate (p. 130.2). Gold nanoparticles are under investigation as adjuncts in diagnostic imaging, as sensitisers for phototherapy, and in delivery systems for drugs and gene therapy. There have been rare reports of hypersensitivity reactions to metallic gold.

Gold chlorides (see below) have been used as a source of gold for medicinal uses.

Homoeopathy

Gold has been used in homoeopathic medicines under the following names: Aurum; Aurum met.; Aurum metallicum; Aur. met.

References.

1. Merchant B. Gold, the noble metal and the paradoxes of its toxicology. *Biologicals* 1998; 26: 49–59.
2. Ehrlich A, Belsito DV. Allergic contact dermatitis to gold. *Cutis* 2000; 65: 323–6.
3. Demann ET, *et al.* Gold as an implant in medicine and dentistry. *J Long Term Eff Med Implants* 2005; 15: 687–98.
4. Han G, *et al.* Multi-functional gold nanoparticles for drug delivery. *Adv Exp Med Biol* 2007; 620: 48–56.
5. Sperling RA, *et al.* Biological applications of gold nanoparticles. *Chem Soc Rev* 2008; 37: 1896–1908.
6. Boisselier E, Astruc D. Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity. *Chem Soc Rev* 2009; 38: 1759–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Oligocure; *Ger.*: Goldlily.

Homoeopathic Preparations. *Austral.*: Respatona Sore Throat; *Austria*: Relax; *Canad.*: Earache; HPB Complex†; Menopause; PMS; Ton 2 Complex†; *Chile*: Rinoplex; Silik; *Cz.*: Gallium; *Fr.*: Abbe Chaupitre no 10†; Abbe Chaupitre no 1†; Kalium Iodatum Complexe No 84†; Rhododendron Complexe No 42†; Sclero-Drainol†; Soludor; Stressdoron; Symphytum Complexe No 48†; *Ger.*: Antihypertonicum N†; Aurum/Lavandula comp.; Aurumarell Kreislauf-Spezifikum; Cor; Crataegus comp; Derivatio H; Derivatio; Disci Bamb; Ginkgo biloba comp; Infekt 1-Injektopas N; Infi-China; Neurodoron; Otofren; Schworocard; Tondinel H; *Neth.*: Gynaelite; *S.Afr.*: Kalium Phos Comp†; *Switz.*: HerBalance; Regenaplex Nr. 24b; Regenaplex Nr. 24c; Regenaplex Nr. 71b; Regenaplex Nr. 79; Regenaplex Nr. 88b.

Gold Chloride

Aurous Chloride; Gold (I) Chloride.
Gold monochloride.
AuCl=232.4
CAS — 10294-29-8; 11118-27-7.
UNII — 15443PR153.

Gold Acid Chloride

Auric Acid; Chloroauric Acid; Gold Acid Tetrachloride; Gold Acid Trichloride; Gold Trichloride Hydrochloride; Hydrochloroauric Acid; Tetrachloroauric (III) Acid.
Hydrogen (SP-4-1)-tetrachloroaurate(1-).
$HAuCl_4$=339.8.
CAS — 16903-35-8 (anhydrous gold acid chloride); 16961-25-4 (gold acid chloride trihydrate); 1303-50-0 (gold acid chloride tetrahydrate).
UNII — 8H372EGX3V.

Gold Trichloride

Auric Chloride; Auric Trichloride; Gold (III) Chloride.
$AuCl_3$=303.3.
CAS — 13453-07-1.

Sodium Tetrachloroaurate

Gold Chloride Sodium; Gold Sodium Chloride; Sodium Chloroaurate (III).
Sodium tetrachloroaurate (III).
$AuCl_4Na$=361.8
CAS — 15189-51-2.
UNII — 7FT6QUT299.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate for homoeopathic preparations.

Ph. Eur. 8: (Sodium Tetrachloroaurate Dihydrate for Homoeopathic Preparations; Natrii Tetrachloroauras Dihydricus ad Praeparationes Homoeopathicas). Orange-yellow, hygroscopic powder or crystals. Very soluble or freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Gold forms several compounds with chlorine depending on its oxidation state. Gold acid chloride and gold trichloride are gold chlorides in which the gold is in the +3 (auric) oxidation state. They have been used as sources of gold for industrial and medicinal purposes. Sodium tetrachloroaurate, the sodium salt of gold acid trichloride, has been used similarly.

Homoeopathy

Gold chloride and its derivatives have been used in homoeopathic medicines under the following names:

- Gold chloride: aurum chloratum; aurum chlor; aurum chlorat; aurum muriaticum
- Sodium tetrachloroaurate: aurum chloratum natronatum; auri et natri chloridum; aurum et natrum muriaticum; aurum muriaticum natronatum; chlorure d'or et de sodium; chlorure d'or jaune; gold chloride, sodium; natrium-goldchlorid; natrium tetrachloroauratum; sodium gold chloride; sodium tetrachloroaurate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Irontona†; Vitatona†.

Homoeopathic Preparations. *Austria*: Aurumheel; *Canad.*: Aurumheel†; *Fr.*: Aurum Complexe No 38†; Cimicifuga Complexe No 21†; Homeodose 8†; Mercurius Solubilis Complexe No 39; Sativol†; Selenium Complexe No 99; Strophantus Compose; Uranthone; Vinicard†; *Ger.*: Acirufan; Aurum-Gastreu S R2; Goldtropfen S; HanoCor N; Infi-Camphora; Infi-China; Lowe-Komplex Nr 10; Myonasan; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; *Hung.*: Aurumheel; Naso-Heel S; *Neth.*: Co-Hypert; Gletar; Phonix Solidago comp; Sativol†; *Switz.*: Gouttes d'Or; Regenaplex Nr. 12; Regenaplex Nr. 71b; *Ukr.*: Aurocard (Аурокард).

Gold Iodide

CAS — 10294-31-2 (gold monoiodide); 13453-24-2 (gold triiodide).
UNII — T1UDV7E51A.

Profile

Iodides of gold (above) include gold monoiodide (aurous iodide; gold (I) iodide) and gold triiodide (auric iodide; gold (III) iodide).

Homoeopathy

Gold iodide, a mixture of gold monoiodide and gold triiodide, has been used in homoeopathic medicine under the following names: Aurum iodatum Aurum jodatum Aurum jodat.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Roth's Rotacard; *Rus.*: Aurum Plus (Аурум-Плюс).

Gossypol

Gosipol; Госсипол.
2,2'-Bis(1,6,7-trihydroxy-3-methyl-5-isopropylnaphthalene-8-carboxaldehyde).
$C_{30}H_{30}O_8$=518.6
CAS — 303-45-7.
UNII — KAV158369O.

Profile

Gossypol is a pigment extracted from cottonseed oil (p. 2180.1). It possesses antispermatogenic activity and has been studied, especially in China, as a male contraceptive. It has also been investigated for its antineoplastic, antiprotozoal, antiviral, and spermicidal activity and has been studied in women in the treatment of gynaecological disorders.

Adverse effects have included fatigue, changes in appetite, gastrointestinal effects, burning sensation of the face and hands, some loss of libido, and persistent oligospermia. Hypokalaemia has occurred.

The pharmacology and therapeutic potential of gossypol have been reviewed.[1] Although controlled studies[2,3] have shown gossypol to be an effective male contraceptive, WHO concluded[4] that gossypol would not be acceptable as a male antifertility drug because of the occurrence of adverse effects such as hypokalaemia and irreversible testicular damage resulting in azoospermia or severe oligozoospermia.

1. Wu D. An overview of the clinical pharmacology and therapeutic potential of gossypol as a male contraceptive agent and in gynaecological disease. *Drugs* 1989; 38: 333–41.
2. Coutinho EM, *et al.* Antispermatogenic action of gossypol in men. *Fertil Steril* 1984; 42: 424–30.
3. Liu G, *et al.* Clinical trial of gossypol as a male contraceptive drug part I: efficacy study. *Fertil Steril* 1987; 48: 459–61.
4. Waites GMH, *et al.* Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. *Int J Androl* 1998; 21: 8–12.

Grape

Grapevine; Rebe; Vigne Rouge; Weinstock; Виноград.
ATC Herb — HC05BW5006 (Vitis vinifera leaf).
UNII — 6X543N684K (grape); 3GOV20705G (wine grape); 3XQ5L209OF (golden raisin); 22E66I250J (Vitis vinifera); R1H893D80E (Vitis vinifera leaf); C34U15ICXA (Vitis vinifera seed).

NOTE. Distinguish from grape bark, Cocillana, p. 1659.2.

Pharmacopoeias. *Fr.* includes Red Vine Extract (Extrait de Vigne Rouge (Sec)), prepared from the leaves. *US* includes Grape Seeds Oligomeric Proanthocyanidins.

USP 36: (Grape Seeds Oligomeric Proanthocyanidins). A fraction of an extract of the ripe seeds of *Vitis vinifera*. It contains not less than 75% of oligomeric proanthocyanidins. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

The seeds and the leaves of the grape, *Vitis vinifera* (Vitaceae), are used in herbal medicine. The dried fruit (raisins) have laxative and demulcent properties.

Many parts of the plant including the fruit skin, seeds, and leaves are used. Both dietary sources and various extracts are promoted for their antoxidant properties in venous insufficiency and capillary impairment, and it has been suggested that they may protect against atherosclerosis.

A standardised red vine leaf extract (AS-195) has been given for the management of chronic venous insufficiency.

Grape seed and grape seed extracts have been included in preparations for peripheral vascular disorders and venous insufficiency and for prophylaxis of cardiovascular disorders. Extracts of grape seed proanthocyanidins, including IH636, are being investigated for a range of other disorders in which antoxidant and free-radical scavenging activity is thought to be beneficial, including cancer prevention, hepatic disorders, radiation-induced fibrosis, cataracts, and macular degeneration, although there is currently little evidence of efficacy.

Resveratrol, a compound present in grapes, (see p. 2603.2) is also promoted as an antoxidant.

Grape seed oil is included in topical preparations.

The fresh and dried fruits of the grape and the leaves are used as foodstuffs.

Review.

1. Bombardelli E, Morazzoni P. *Vitis vinifera* L. *Fitoterapia* 1995; 66: 291–317.
2. Nassiri-Asl M, Hosseinzadeh H. Review of the pharmacological effects of *Vitis vinifera* (grape) and its bioactive compounds. *Phytother Res* 2009; 23: 1197–1204.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flebo Ikatral; Ikatral; Mikonos; Viticalm; *Austria*: Antistax; Pedopur; *Braz.*: Antistax; Celox†; Radiree; Vinera; *Chile*: Endotelon†; Uvanox; Viticalm; *Cz.*: Antistax; *Fr.*: Endotelon; *Ger.*: Antistax; *Hung.*: Endotelon; *Ital.*: Antistax; Perfluxi; *Mex.*: Antistax; *Pol.*: Endotelon†; *Rus.*: Antistax (Антистакс); Endotelon (Эндотелон); *Singapore*: French Parad'ox Plus; *Spain*: Antistax; *Switz.*: Antistax; *Turk.*: Antistax; *UK*: Antistax; *Ukr.*: Endotelon (Эндотелон).

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; Clstidac; CVP Cellulite; HSN; Ikatral Periferico; Laxiruela; Procto-Ikatral;

Austral.: Anthogenol; Antioxidant Forte Tablets†; Arthro-Eze; Atopiclair†; Bio ACE Excell; Flavonoid Complex; Homme-F; Joint Base; PM Joint-Care; Pygno-Vite†; Radiance; ResveratoX; Vein Relief; Vitanox; Zellulean with Escin†; *Austria*: Hepatodoron; *Canad.*: Immune Formula†; Proflavanol 90†; *Chile*: Celltech; Seresis; *Fr.*: Anthylline†; Anti-oxydant F4; Blue Berry; Cledist; Corvitec; Derm; Diveine; Imedeen Prime Renewal†; Imedeen Time Perfection†; Mediflor Circulation du Sang No 12†; Nutrof Total; Omegaline Solaire; Ophtalmine†; Opo-Veinogene; Pharyndol; Pharyndol; Phlebosedol†; Tisane Provencale no 3†; Veinophytum†; *Ger.*: Hepatodoron; *Hong Kong*: Proflavanol†; *India*: Calorex; Dayvital; Diakof; Ecome-LY; Eldervit-ZC; Elgrape; Elmega-3; Elnutra-M; Geriforte; Hair-stim-HGF; Koflet; L-Bex; Lycobond; Lycominvit; Lyconerve; Morvit; Natoz; Nislutin; Orymax; Orymax; Oxitard; Oxy-Grape; *Indon.*: Antox; Atopiclair; Kapset; Lanaven Plus†; Legres; Legreskin; Liproqy; Lycoq†; Lyphen; Noros; Oxan; Proview; Resvica†; *Israel*: Atopiclair; Xclair; *Ital.*: Angiovein; Betaeffe Complex; Blunorm; Capill; Deproctol; Deroidal; DMS Control; Flavion; Mirtilux; Neosulfur†; Traumaven; Venalta; Venalta; Visu-len; Visu-ton; Vitreoclar; Zeadema Crono; Zeadema; *Malaysia*: Glow; Proflavanol†; Seresis; *Mex.*: Proflavanol; Seresis; *Mon.*: Fluon+; *Philipp.*: Gloww; *S.Afr.*: Hepatodoron†; *Singapore*: Atopiclair; Bio-Taches Masque†; Bio-Taches†; Cardio Cocktail; Claricof; Glow; Proflavanol†; Scar Esthetique; Seresis†; *Swed.*: Vitadoron; *Switz.*: Hepatodoron; *UK*: Atopiclair; Xclair; *Ukr.*: Artritosamin (Артритозамин); Bon-Apetit (Бон-Аппетит); Imunin (Иммунин)†; Perfectil Plus (Перфектил Плюс); Vitrum Beauty Elite (Витрум Бьюти Элит); Vitrum Beauty Q10 (Витрум Бьюти Q10)†; *USA*: Atopiclair; Cardio Tone; Immunicare; Protegra; Pycnogenol Plus.

Homoeopathic Preparations. *Canad.*: Formula CI 207†; Formula HEPA†; Formula Homeo QR 209†.

Graphite

Black Lead; Mineral Carbon; Plumbago.
CAS — 7782-42-5.
UNII — 4QQN74LH4O.

NOTE. Plumbago, as well as being a synonym for graphite, may be used to refer to lead ores and to a genus of flowering plants (the leadworts).

Profile

Graphite is a crystalline form of carbon containing a small amount of iron and other minerals. Graphite is used as a drawing material, and when mixed with a clay binder, it forms the core in pencils commonly referred to as 'lead' pencils. It also has industrial uses. Exposure to graphite dust can lead to respiratory disorders.

Homoeopathy

Graphite has been used in homoeopathic medicines under the following names: graphites; plumbago.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Elimitona Slim & Detox; Homoderma; *Austria*: Acidum picrinicum Med Complex†; Crimax; Erbiode Akne; Gracil; *Canad.*: Adrisin†; Endoteel†; Execalm†; Ikoplex 11 Digestion Aid†; *Chile*: Bioactiv F; Bioactiv Q; Ikoplex No 7; Lessfat; *Fr.*: Abbe Chaupitre no 22†; Abbe Chaupitre no 23†; Slimum†; Veino-Drainol†; *Ger.*: Derma-Plantin†; Dermi-cyl L Ho-Len-Complex; Ekzem-Entoxin N; Hautfunktionstabletten N; Hautfunktionstropfen N; Otofren; Steiroderm; *Neth.*: Cutis comp; Habifac; *Rus.*: Psorilom (Псорилом); Urtica-Plus (Уртика-Плюс); *Switz.*: Exsepta; Regenaplex Nr. 24c Regenaplex Nr. 25a.

Gravel Root

Joe Pye Weed; Purple Boneset; Queen of the Meadow; Ratz de eupatorio; Посконник Пурпуровый (*Eupatorium purpureum*).
UNII — 0VYGSPVNSO (Eupatorium purpureum).

NOTE. Distinguish from Boneset, *Eupatorium perfoliatum* (see p. 2459.1). Boneset is also used as a common name for *Symphytum officinale* (see Comfrey, p. 2484.2). The name Queen of the Meadow has also been applied to Meadowsweet (p. 2550.2).

Profile

Gravel root is the root of *Eupatorium purpureum* (*Eutrochium purpureum*) (Compositae) and has diuretic, antilithic, and antirheumatic properties. It is used for renal and urinary calculus and other urinary-tract disorders, and has also been used for gout and rheumatism.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Backache.

Homoeopathic Preparations. *Canad.*: Goldenrod Combination†; *Ger.*: Cysto-Gastreu S R18; *Neth.*: Cysto-Gastreu R18.

Greater Celandine

Celidonia; Chélidoine; Chelidonii Herba; Chelidonium; Hierba golondrinera; Hierba verruguera; Keltamo; Schöllkraut; Skelört; Tetterwort; Ugniažolių žolė; Vérehulló fecskefű; Vlaštovičníková nať; Ziele glistnika; Гистогел большой.
ATC Herb — HN02BW5002 (Chelidonium majus: root); HA05AW5004 (Chelidonium majus: herb).
UNII — 7E889U5RNN (Chelidonium majus).

NOTE. The name Tetterwort has also been used for Sanguinaria (p. 2610.1).

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

Ph. Eur. 8: (Greater Celandine). The dried, whole, or cut aerial parts of *Chelidonium majus* collected during flowering. It contains a minimum of 0.6% of total alkaloids expressed as chelidonine ($C_{20}H_{19}NO_5$ = 353.4), calculated with reference to the dried drug.

Uses and Administration

Greater celandine has sedative and spasmolytic properties and the aerial parts are used for liver, biliary, and gastrointestinal disorders, and have also been used for respiratory-tract disorders. The latex has been used externally for warts and other skin conditions.

Homoeopathy

Greater celandine has been used in homoeopathic medicines under the following names: Chelidonium; Chelidonium majus; Chelidonium maj; Chelidonium majus, radix; Chelidonium, rad; Chelidonium, Flos; Chelidonium majus e floribus; Che. maj.

Effects on the liver. References.

1. Benninger J, *et al.* Acute hepatitis induced by greater celandine (Chelidonium majus). *Gastroenterology* 1999; **117**: 1234–7.
2. Stickel F, *et al.* Acute hepatitis induced by Greater Celandine (Chelidonium majus). *Scand J Gastroenterol* 2003; **38**: 565–8.
3. Moro PA, *et al.* Hepatitis from Greater celandine (*Chelidonium majus* L.): review of literature and report of a new case. *J Ethnopharmacol* 2009; **124**: 328–32.

Adverse Effects

Greater celandine has been reported to cause acute cholestatic hepatitis, stomatitis, gastroenteritis, and dermatitis. Fatalities have occurred after haemorrhagic gastritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Paverysat forte N†.

Multi-ingredient Preparations. *Arg.*: Quelodin F; *Austral.*: Berberis Complex†; Extralife Liva-Care†; Toxicol; *Austria*: Choleodoron; Iberogast; *Belg.*: Aporil; *Cz.*: Iberogast; *Fr.*: Nitrol†; *Ger.*: Chol-Kugeletten Neu†; Cholhepan N; Gallemolan forte†; Iberogast; *Hong Kong*: Hepatofalk Planta†; Hepatofalk†; *Hung.*: Depsorin; Herpesil; Iberogast; Vesevedo; *Indon.*: Lanagogum; *Neth.*: Iberogast; *Pol.*: Artecholin†; Artecholwex†; Chelicur; Cholavisol; Cholitol; Enterosol; Iberogast; Neoazarina; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Złożony†; Syrop Sosnowy Złożony; *S.Afr.*: Choleodoron†; *Singapore*: Hepatofalk Planta†; *Spain*: Iberogast; Nitroina; *Swed.*: Iberogast; *Switz.*: Choleodoron; Iberogast; *Ukr.*: Iberogast (Иберогаст); *Venez.*: Demerung.

Homoeopathic Preparations. *Austral.*: IBS Eze; Sedatif†; Stomach Calm; *Austria*: Galstena; Lymphdiaral; Taraxacum Med Complex; *Canad.*: Carduus Plex†; Chelidonium Plex†; Choleodoron†; Dandelion Combination†; Digestion; Formula FV 213; Formula Homeo QR 209†; Headache & Migraine L77; Hepar Compositum; Sedatil; *Cz.*: Hepeel; Sedatif PC; *Fr.*: Abbe Chaupitre no 35†; Adenocynesine†; Amanita Complexe No 75; Boripharm No 15†; Chelidonium Compose; Choleodoron; Conium Complexe No 36†; Digeoslor; Gastro-Drainol†; Grindelia Complexe No 58; Hepatodrainol; Hepatopan†; Hydrastis Compose; Juniperus Complexe No 6; Kreosotum Complexe No 62; L 114; Phapax; Sedatif PC; Yucca Complexe No 110; *Ger.*: Chelidonium comp; Chol-Do; Choleodoron†; Cholo 2-injektopas; Derivatio H; Derivatio; Flenin; Galloselect; HanoHepan; Hepa-Gastreu N R7; Hepa-Loges N; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Homviohepan; Infihepan; Leber-Galletropfen; Lymphdiaral; Marianon Hepar; Phonix Silybum spag; Phyto-L; Phytocortal; Rufebran heparo†; Spasmo-Bomaleb†; *Hung.*: Hepeel; Sedatif; *Neth.*: Actelite; Chelidonium-Homaccord N; Choleodoron; Collite; Echilite; Hepa-Gastreu R7; Hepalite; Hepatodrainol†; Lymphdiaral; Sedatif PC; *Port.*: Hepatodrainol; Sedatif PC; *Rus.*: Berberis-Plus (Берберис-Плюс); Galstena (Галстена); Helidonium-Plus (Хелидониум-Плюс); Homeostres (Гомеострес); *Switz.*: Hepeel; metaheptachol; Regenaplex Nr. 79; Sedatif PC; *UK*: Choleodoron; *Ukr.*: Choledius (Холедиус); Galstena (Галстена); Sedatif PC (Седатив ПЦ); *USA*: Preferred Remedies Detoxin.

Green-lipped Mussel

Extracto de mejillón de labios verdes; Зеленого Губчатого Моллюска.
UNII — 1LS332YQ7U.

Profile

An extract from the green-lipped mussel *Perna canaliculus* (Mytilidae), stated to contain omega-3 polyunsaturated fatty acids, amino acids, fats, carbohydrates, and minerals, has been promoted for the treatment of rheumatic disorders including rheumatoid arthritis (p. 13.2). It has also been tried in asthma.

Musculoskeletal and joint disorders. Reviews of the investigation of green-lipped mussel in the treatment of arthritis have not revealed conclusive evidence of its usefulness,[1-4] although it might be of benefit in osteoarthritis when taken with paracetamol or NSAIDs.[3]

1. Li Wan Po A, Maguire T. Green-lipped mussel. *Pharm J* 1990; **244**: 640–1.
2. Cobb CS, Ernst E. Systematic review of a marine nutriceutical supplement in clinical trials for arthritis: the effectiveness of the New Zealand green-lipped mussel *Perna canaliculus*. *Clin Rheumatol* 2006; **25**: 275–84.
3. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf (accessed 16/08/10)
4. Brien S, *et al.* Systematic review of the nutritional supplement *Perna canaliculus* (green-lipped mussel) in the treatment of osteoarthritis. *Q J Med* 2008; **101**: 167–79.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Lyprinol; *UK*: Healtheries Musseltone; Lyprinol; Mobilyzer; Oceantone; Seatone; Supplex.

Multi-ingredient Preparations. *Ital.*: Osteoclar; *UK*: Healtheries Musseltone & Glucosamine.

Griffonia Simplicifolia

Гриффония.
UNII — 8M5FTG8LCS (Griffonia simplicifolia); LUS5142TMY (Griffonia simplicifolia seed).

Profile

The leaf, stem, and twigs of *Griffonia simplicifolia* (Fabaceae) have been used for a variety of disorders in its native West Africa. It is included in herbal and nutritional supplements. It is a source of lectins and has insecticidal properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Safralite; *Ital.*: Brioplus; Calmason; Climil Complex; Ginecast; Spm-OK.

Grindelia

Gum Plant; Gumweed; Tar Weed; Гринделия Крупная (*Grindelia camporum*).
ATC Herb — HR05WA5016 (Grindelia humilis: herb); HR05WA5015 (Grindelia camporum: herb); HR03WX5004 (Grindelia camporum: herb).
UNII — 1D8ONAZ6AL (grindelia); E9Q71VSJ1S (Grindelia robusta).

Pharmacopoeias. In *Fr.* which allows *Grindelia camporum*, *G. humilis*, *G. robusta*, and *G. squarrosa*.

Profile

Various *Grindelia* spp. (Asteraceae) have been included in herbal preparations used for respiratory-tract disorders.

Homoeopathy

Grindelia has been used in homoeopathic medicines under the following names: Grindelia robusta; Grind. ro.

References.

1. Canavan D, Yarnell E. Successful treatment of poison oak dermatitis treated with *Grindelia* spp. (Gumweed). *J Altern Complement Med* 2005; **11**: 709–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel; *Austral.*: Asa Tones†; Euphorbia Complex†; PulmaCo; ResCo; *Chile*: Ramistos; *Fr.*: Coquelusedal Nourrissons; Coquelusedal Paracetamol Nourrissons†; Coquelusedal Paracetamol; Coquelusedal; Ephydion†; Neo-Codion; Neo-Codion; Pectoflorine†; Vegetoserum; *Hung.*: Bronchicum; Bronchicum; *Indon.*: Pec-

tum; *Ital.*: Broncosedina; Broncosedina; Cistefi; *Neth.*: Bronchicum; *Pol.*: Bronchicum Eliksir†; Echinasal; *Rus.*: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Neo-Codion (Нео-Кодион)†; Neo-Codion Babies (Нео-Кодион Для Младенцев)†; *Spain*: Pazbronquial; *Switz.*: Neo-Codion N; Nican†; *Venez.*: Novacodin.

Homoeopathic Preparations. *Canad.*: Arum Triphyllum Plex†; *Fr.*: Arum Triphyllum Compose; Grindelia Complexe No 58; *Ger.*: A-Bomin; Aralis; Asthmakhell N; Bronchi-Do; Bronchopas; Bronchosyx comp; Drosera-Weliplex†; Neolin-Entoxin; Pulmo Bronchialcomplex; Pulmo Bronchialcomplex; Pulmorell; Santa Flora S; *Neth.*: Allgeno spag; Asakell; Asthmakhell†.

Ground Ivy

Ale-hoof; Gundelrebe; Gundermann; Hiedra terrestre; Lierre Terrestre; Nepeta Glechoma; Бупра Плющевидная.
UNII — L6O7WQK912 (Glechoma hederacea).

Pharmacopoeias. In *Chin.* and *Fr.*

Profile

Ground ivy, the aerial parts of *Glechoma hederacea* (*Nepeta hederacea*) (Labiatae) has been used for respiratory-tract and gastrointestinal disorders.

Homoeopathy

Ground ivy has been used in homoeopathic medicines under the following names: Glechoma; Glechoma hederacea.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Gerard House Water Relief Tablets; Water Naturtabs.

Homoeopathic Preparations. *Canad.*: Toxex; *Hung.*: Toxex; *Neth.*: Allgeno spag; Habifac; Opsonat; Speci-chol; Toxex; *Switz.*: Regenaplex Nr 28a.

Guaiacum Resin

Guaiac; Guaiacum; Guajakharz; Gwajakowa żywica; Resina de guayaco; Гваяковая Смола.
CAS — 9000-29-7.
UNII — N0K2Z502R6 (Guaiacum officinale *resin*); *03C8A0DFJ8* (*guaiac*).

Profile

Guaiacum resin is obtained from guaiacum wood (lignum vitae; *Guaiacum officinale* or *G. sanctum*) (Zygophyllaceae) and has been used in the treatment of rheumatism. It is used in herbal medicine.

Guaiacum resin is used in the detection of occult blood in the faeces. The accuracy of the guaiacum test has been questioned and some drugs may interfere with the result.

Homoeopathy

Guaiacum resin has been used in homoeopathic medicines under the following names: Guaiacum; Guajacum; Guaic.

References.

1. Ko CW, *et al.* Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003; 115: 111–14.
2. Tannous B, *et al.* Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. *Clin Chim Acta* 2009; 400: 120–2.
3. Loitsch SM, *et al.* Stool test for colorectal cancer screening—it's time to move! *Clin Lab* 2008; 54: 473–84.
4. Guittet L, *et al.* Comparison of a guaiac and an immunochemical faecal occult blood test for the detection of colonic lesions according to lesion type and location. *Br J Cancer* 2009; 100: 1230–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Boswellia Compound; *Ital.*: Tisana Kelemata; *Switz.*: Pommade au Baume; *UK*: Gerard House Reumalex; Rheumatic Pain Relief; Rheumatic Pain Remedy; Rheumatic Pain.

Homoeopathic Preparations. *Austria*: Anfokali; Globuli gegen Halsweh Nr 1; *Canad.*: Arthritis Pain Formula; *Chile*: Artroplex; *Ger.*: Cefadolor H†; Homvioartrin; Infekt-Komplex L Ho-Fu-Complex; Tonsipret; *Hung.*: Anfokali; *Neth.*: Apo-Rheum†; Reudol; *Rus.*: Tonsipret (Тонзипрет); *Ukr.*: Tonsipret (Тонзипрет).

Guaiazulene

Gayazulen; Guayazileno; Gwajazulen; Гвайазулен.
1,4-Dimethyl-7-isopropylazulene.
$C_{15}H_{18}$=198.3
CAS — 489-84-9.
ATC — S01XA01.
ATC Vet — QS01XA01.
UNII — 2OZ1K9JKQC.

Profile

Guaiazulene has been reported to have anti-allergic, anti-inflammatory, antipyretic, and antiseptic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Azulon; *Austria*: Azulenal; *Cz.*: Ophthalmo-Azulen; *Fr.*: Azulene†; *Hung.*: Azulenol; Garmastan; *Turk.*: Garmastan.

Multi-ingredient Preparations. *Arg.*: Sodorant; *Austria*: Piniment; Spasmo Claim†; Thrombocid; *Cz.*: Dermazulen; Ophthalmo-Septonex; Pinosol; Pityol; *Fr.*: Cicatryl; Pepsane; *Ger.*: Thrombocid; *Hong Kong*: Thrombocid; *Hung.*: Pinosol; *Israel*: Aronal Forte; *Mex.*: Pepsane; *Pol.*: Pinosol†; *Port.*: Thrombocid; *Rus.*: Pepsane-R (Пепсан-Р); Pinosol (Пиносол); Pinovitum (Пиновитум); *Switz.*: Bain extra-doux; *Ukr.*: Pepsane (Пепсан); Pinosol (Пиносол)†.

Guanidine Hydrochloride

Carbamidine Hydrochloride; Guanidina, hidrocloruro de; Guanidyny chlorowodorek; Iminourea Hydrochloride; Гуанидина Гидрохлорид.
$CH_5N_3.HCl$=95.53
CAS — 113-00-8 (guanidine); 50-01-1 (guanidine hydrochloride).
UNII — 3YQC9ZY4YB.

Profile

Guanidine hydrochloride enhances the release of acetylcholine from nerve terminals. It has been given orally to reverse neuromuscular blockade in patients with botulism (p. 2380.2), but its efficacy has not been established. Guanidine hydrochloride has also been tried in Eaton-Lambert myasthenic syndrome (p. 684.1) and other neurological disorders, but its use has been associated with bone-marrow suppression in some patients.

References.

1. Kaplan JE, *et al.* Botulism, type A, and treatment with guanidine. *Ann Neurol* 1979; 6: 69–71.
2. Critchley EMR, *et al.* Outbreak of botulism in North West England and Wales. *Lancet* 1989; ii: 849–53.
3. Neal KR, Dunbar EM. Improvement in bulbar weakness with guanozan in type B botulism. *Lancet* 1990; 335: 1286–7.
4. Oh SJ, *et al.* Low-dose guanidine and pyridostigmine: relatively safe and effective long-term symptomatic therapy in Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 1997; 20: 1146–52.

Guanosine

Guanine Riboside; NSC-19994; Vernine; Гуанозин.
2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6(1*H*)-one.
$C_{10}H_{13}N_5O_5$=283.2
CAS — 118-00-3.
UNII — 12133JR80S.

Profile

Guanosine is an endogenous guanine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Guanosine is included in preparations for peripheral and cerebral vascular disorders and myopathies; guanosine monophosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Vitacid†; *Spain*: Nutracel.

Guggul

Guggal; Guggulu; Gugul; Indian Bdellium; Mukul Myrrh.
UNII — 34969JX79R.

Pharmacopoeias. In *US.*

USP 36: (Guggul). The oleo-gum-resin obtained by incision or produced by spontaneous exudation from the stem and branches of *Commiphora wightii*. Store at 8 degrees to 15 degrees. Protect from light and moisture.

Profile

Guggul is the oleo-gum resin obtained from *Commiphora wightii* (*C. mukul*; *Balsamodendrum wightii*; *B. mukul*) (Burseraceae), a tree native to India. Guggul extracts have long been used in Ayurvedic medicine. Guggulipid (guglip; guglipid; gugulipid) is a standardised ethyl acetate extract of the gum resin that is produced commercially and used in dietary supplement preparations for lipid disorders, weight loss, and arthritis. The ketonic steroids *E*- and *Z*-guggulsterone are believed to be the bioactive compounds in guggulipid and other guggul extracts; they are thought to inhibit cholesterol synthesis through antagonism of the farsenoid X and bile-acid receptors.

Guggul should not be confused with myrrh (p. 2566.1) to which it is related.

Although plausible mechanisms of action have been shown for guggulsterones, the active plant sterols in the dietary supplement guggulipid, there is no scientific evidence to support use in practice to improve lipid profiles.[1-4]

1. Szapary PO, *et al.* Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial. *JAMA* 2003; 290: 765–72.
2. Sahni S, *et al.* Guggulipid use in hyperlipidemia: case report and review of the literature. *Am J Health-Syst Pharm* 2005; 62: 1690–2.
3. Ulbricht C, *et al.* Natural Standard Research Collaboration. Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. *Complement Ther Med* 2005; 13: 279–90.
4. Nohr LA, *et al.* Resin from the mukul myrrh tree, guggul, can it be used for treating hypercholesterolemia? A randomized, controlled study. *Complement Ther Med* 2009; 17: 16–22.

Adverse effects. References.

1. Klötke A, *et al.* Allergic contact dermatitis to guggul extract contained in an anticellulite gel-cream. *Contact Dermatitis* 2006; 54: 226–7.
2. Salavert M, *et al.* Allergic contact dermatitis to guggul in a slimming cream. *Contact Dermatitis* 2007; 56: 286–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Flexi-muv†; Karnim; *Malaysia*: Rumalaya; *Rus.*: Pilex (Пайлекс).

Pharmacopoeial Preparations

USP 36: Guggul Tablets; Native Guggul Extract; Purified Guggul Extract.

Gutta Percha

Gummi Plasticum; Gutapercha; Gutt. Perch.; Гутаперча.
ATC Herb — HA01AD5001 (Palaquium gutta *gum*).
UNII — 6Z98Z8O1D0.

Pharmacopoeias. In *US.*

USP 36: (Gutta Percha). The coagulated, dried, purified latex of the trees of the genera *Palaquium* and *Payena* and most commonly *Palaquium gutta* (Sapotaceae). It occurs in lumps or blocks of variable size; externally brown or greyish-brown to greyish-white in colour; internally reddish-yellow or reddish-grey and having a laminated or fibrous appearance. It is flexible but only slightly elastic. Has a slight, characteristic odour. Insoluble in water; partly soluble in carbon disulfide, in turpentine oil, and in benzene; about 90% soluble in chloroform. Store under water. Protect from light.

Profile

Gutta percha has been used in various dressings. In dentistry, gutta percha has been used as a filling material and as the basis of compounds for taking dental impressions.

Haematoporphyrin

Hematoporfirina.
$C_{34}H_{38}N_4O_6$=598.7
CAS — 14459-29-1.

Profile

Haematoporphyrin is an iron-free red pigment obtained from haematin. It is an ingredient of preparations promoted as tonics, particularly for the elderly, and has been used in the treatment of depression. Derivatives of haematoporphyrin are used as photosensitisers in the photodynamic therapy of malignant neoplasms (see Porfimer Sodium, p. 849.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Hemedonine.

Multi-ingredient Preparations. *Austria*: KH3; *Chile*: Actebral; *Gr.*: KH3; *Hong Kong*: KH3; *Ital.*: Porfirin 12; Tonogen; *NZ*: KH3; *Thai.*: KH3†.

Hamamelis

Amamelide; Csodamogyorólevél (hamamelis leaf); Hamamelių lapai (hamamelis leaf); Hamamelidis; Hamamelidis folium (hamamelis leaf); Hamameliksenlehti (hamamelis

leaf); Hamamélis de virginie; Hamamélis, feuille d' (hamamelis leaf); Hamamelisblad (hamamelis leaf); Trollhassel; Vilínový list (hamamelis leaf); Virginsk Troldnød; Witch Hazel; Zauberhasel; Zaubernuss; Гамамелис.

ATC Herb — HD03WA5004 (Hamamelis virginiana *leaf*); *HC05AW5003* (Hamamelis virginiana *leaf*); *HD03WX5007* (Hamamelis virginiana *leaf with twig*); *HD03WA5003* (Hamamelis virginiana *bark*).

UNII — V663Q8TEFU (Hamamelis virginiana); *IH3063S9MY* (Hamamelis virginiana *bark*); *222MYC9QUV* (Hamamelis virginiana *flower water*); *T07UT161SV* (Hamamelis virginiana *leaf*); *8FP93ED6H2* (Hamamelis virginiana *leaf water*); *T7S323PKJS* (Hamamelis virginiana *root bark/stem bark*); *UDA30A2JJY* (Hamamelis virginiana *top*); *NT00Y05A2V* (Hamamelis virginiana *top water*); *I01I4J0U34* (Hamamelis virginiana *twig water*).

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

Ph. Eur. 8: (Hamamelis Leaf). The whole or cut dried leaves of *Hamamelis virginiana* containing not less than 3% tannins, expressed as pyrogallol ($C_6H_6O_3$ = 126.1), calculated with reference to the dried drug. Protect from light.

USP 36: (Witch Hazel). A clear, colourless distillate prepared from recently cut and partially dried dormant twigs of *Hamamelis virginiana*. pH between 3.0 and 5.0. Store in airtight containers at a temperature not exceeding 40 degrees.

Profile

Hamamelis has astringent properties and contains gallic acid, a bitter principle, and a trace of volatile oil. It is used in preparations for the symptomatic relief of haemorrhoids (p. 1808.1). Hamamelis water is used as a cooling application and has been applied as a haemostatic.

Hamamelis is used in herbal preparations for a variety of disorders.

Homoeopathy

Hamamelis has been used in homoeopathic medicines under the following names: Hamamelis virginiana; Hamamelis, Folium; Hamamelis virginiana e foliis; Hamamelis virginiana ex cortice summitatibusque; Hamamelis virginica; Ham. virg.

General references.

1. WHO. Folium et Cortex Hamamelidis. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/14.html (accessed 04/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Optrex; ***Austria***: Hametum; ***Braz.***: Hemoproct; ***Canad.***: Nik + Aid†; Optrex; ***Fr.***: Optrex; ***Ger.***: Faktu mit Hamamelis; Haenal Hamamelis; Hametum; Posterine; ***Hong Kong***: Optrex; ***Irl.***: Optrex; ***Ital.***: Acqua Virginiana; Derminiol; Optrex; ***Malaysia***: Optrex; ***Mex.***: Tia Puppy; ***NZ***: Optrex; ***Pol.***: Phloderm†; ***Port.***: Optrex; ***Singapore***: Optrex; Preparation H; ***Spain***: Derminiol†; Hemo Derminiol†; Optrex; Suaviplant†; ***Switz.***: Hametum; Mavena Anal-Gen; Optrex; ***Thai.***: Optrex; ***Turk.***: Hametan; ***UK***: Optrex; Preparation H Clear Gel; Witch Doctor; Witch Sunsore; ***USA***: A-E-R; Neutrogena Drying.

Multi-ingredient Preparations. ***Arg.***: Astriluge; Dermacne; Domuderm; Ecnagel; Esculeol P; Lavandula Oligoplex; Manzan; Varicura; Venoful; VNS 45; Xyloprocto Toallas; ***Austral.***: Anusol†; Gentlees; Hemocane; Optrex Medicated†; ***Austria***: Arnicet†; Inotyol; Inotyol; Mirfulan; Sulgan 99; ***Belg.***: Hemorhinol†; Purigel Crisp†; Rectovasol; ***Braz.***: Hemodotti†; Hemofleb; Higicler; Malvatricin Natural Organic†; Proctosan; Visionom; ***Canad.***: Onrectal†; Preparation H-PE Gel; Tucks†; ***Chile***: Keracnyl Stop Bouton; Normaderm Barra de Limpieza; Normaderm Concentrado Activo; Normaderm Gel de Limpieza; Proctoplex; ***Fr.***: Anastase; Anthyline†; Aphloine P; Climaxol; Diveine; Evaroset†; HEC; Histo-Fluine P; Inotyol; Jouvence de l'Abbe Soury; Jouvence de l'Abbe Soury; Keracnyl eau nettoyante†; Keracnyl stop bouton; Mediflor Circulation du Sang No 12†; Ophtalmine†; Pastilles Monleon†; Phlebosedol†; Phytomelis; Santane V_3†; Tisane Provencale no 3†; Veinostase; ***Ger.***: Aescusan†; Eulatin NH; Mirfulan; Trauma-cyl†; Varicylum-S†; Weleda Hamorrhoidalzapfchen; Weleda Hauttonikum†; ***Hong Kong***: Eye Glo Plus; ***Indon.***: Oculosan; ***Irl.***: Optrex Clear Eyes; ***Israel***: Derma Care; Inotyol; ***Ital.***: Altacura Ipragocce; Centella Complex; Centella Complex; Centeril H; Centeril H; Decon Ovuli; Dermilia Flebozin†; Dermitina; Eulux; Fito Stomygen†; Gefion; Ginoxil Ecoschiuma; Intim; Iridil; Mirtiros; Nevril; Proctopure; Sacnel; Salviette H; Steril Zeta; Venactive; Venalta; ***Malaysia***: Dermaheal DeAkni; ***Mex.***: Almodin; Prespir; Supranettes Naturalag; ***Mon.***: Fluon+; Fluon; ***Neth.***: Bioforce; ***NZ***: Optrex Red-Eye Relief; ***Port.***: Hemofissural; ***S.Afr.***: Lotio Pruni Comp cum Cupro†; Stibium Comp†; ***Singapore***: Nu-Derm Toner; Stop-Itch Plus; ***Spain***: Banoftal†; Ojosbel Azul†; Ojosbel; Solucion Schoum; ***Switz.***: Baume Dalet; Collypan; Haemolan†; Hametum-N; HEC†; Mavena Proctal-Gen†; Oculosan; Optrex compresses†; Suppositoires contre les hemorroides; Venadoron; ***Thai.***: Opplin; ***Turk.***: Symphosan; ***UK***: Adiantine; Eye Dew; Heemex; Lacto Calamine; Lacto Calamine; Modern Herbals Pile; Optrex Red Eyes; Supranettes; Swarm; Tea Tree & Witch Hazel Cream; Varicose Ointment; Vital Eyes; ***USA***: Bioflex; Clearasil Double Clear; Flexgen; Preparation H Cooling Gel; Tucks; ***Venez.***: Camolyn Plus; Camolyn; Flucirac.

Homoeopathic Preparations. ***Austria***: Hamamelis-Homaccord; Traumeel; Venodril; Vensa; ***Canad.***: Avenoc†; Cruroheel S†; Formula CI 207†; Formula Homeo QR 209†; Hae 1 Complex†; Lympatox; Traumeel; ***Chile***: Arnica Hamamelis Compuesta; Calcarea fluor Compuesta; Variplant; Variplex; ***Cz.***: Traumeel; ***Fr.***: Abbe Chaupitre no 15†; Abbe Chaupitre no 20†; Abbe Chaupitre no 64†; Aesculus Complexe No 103; Aesculus Compose; Avenoc; Calendula Complexe No 89; Hamamelis Compose; Homeodose 20†; L 28; Poconeol no 51; Pulviplasmine†; Sepia Compose; Thlascose†; Vascoflor; Veino-Drainol†; Veinosium†; ***Ger.***: Agnus castus comp†; EAP-61; Haemorrhoid-Gastreu N; Heweven Complex; Infihepan; ISO-Augentropfen C; Pesendorfer; phono Ven; Regenaplex Haut W; Reproven N; Ruta-Gastreu N R55; Secale-Gastreu; Traumeel S; Varicylum N; Venen-Komplex Ho-Pu-Complex; Veno-Injektopas; Venokatt; Venorell; Wibotin HM; ***Hung.***: Traumeel; ***Neth.***: Aesculus Comp; Ambheel; Hemorrolite; Homeocare Vasco; Omnilite; Traumeel S; Venafleur; ***Port.***: Avenoc; Homeodent†; ***Rus.***: Mercure-Plus (Меркур-Плюс); Paeonia-Plus (Пеония-Плюс); Traumeel S (Траумель С); Vensa (Венза); ***S.Afr.***: Achillea Compt†; Hamamelis Comp†; Traumeel S; ***Switz.***: Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 31b; Regenaplex Nr. 31c; Regenaplex Nr. 49a; Regenaplex Nr. 59b; Traumeel; ***UK***: Haemorrhoid Cream; ***Ukr.***: Traumeel S (Траумель С); ***USA***: Succus Cineraria Maritima†; Traumeel; ***Venez.***: Traumeel.

Pharmacopoeial Preparations

USP 36: Witch Hazel.

Harmaline

Harmalina.

3,4-Dihydroharmine.

$C_{13}H_{14}N_2O$=214.3

CAS — 304-21-2.

UNII — CN5814TOET.

Description. Harmaline is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of harmaline or preparations containing harmaline:

Caapi; Huasca; Purga, la; Vine; Yage.

Harmine

Harmina; 7-Methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole; Хармин.

$C_{13}H_{12}N_2O$=212.3

CAS — 442-51-3.

UNII — 4FHH5G48T7.

Description. Harmine is an alkaloid obtained from peganum, the dried seeds of *Peganum harmala* (Zygophyllaceae), also known as Syrian rue.

Harmine is identical with an alkaloid known as banisterine or telepathine obtained from *Banisteriopsis caapi* (Malpighiaceae).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of harmine or preparations containing harmine:

Rue.

Profile

Harmine and harmaline are the main active principles of a hallucinogenic drink, known in South American regions as 'ayahuasca', 'caapi', or 'yagé', that is made from closely related plants of the family Malpighiaceae. They have no therapeutic use.

Hedge Mustard

Erysimum; Hederichkraut; Herbe aux Chantres; Scrambling Rocket; Singer's Plant; St. Barbara's Hedge Mustard; Thallcroc; Vägsenap; Wegrauke; Wegsenf; Гулявник Лекарственный.

NOTE. The name English Watercress has been applied to Hedge Mustard, but it is more usually applied to *Nasturtium officinalis*.

Profile

The aerial parts of hedge mustard *Sisymbrium officinale* (*Erysimum officinale*) (Brassicaceae), have been used in herbal medicine mainly for sore throats and coughs. It has been given orally for respiratory, urinary, and gastrointestinal disorders. It is reported to contain cardioactive glycosides.

Hedge mustard also has culinary uses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Euphon; ***Fr.***: Drill Enrouement; Euphon; Voxyl†; ***Port.***: Euphon; ***Singapore***: Euphon.

Multi-ingredient Preparations. ***Fr.***: Activox; Clarix Toux Seche†; Euphon; Humex Gorge Irritee†; Pectoflorine†; Pholcodyl†; Polery; Polery; Vocadys; ***Malaysia***: Euphon; ***Port.***: Euphon; ***Rus.***: Cardiovalen (Кардиовален).

Homoeopathic Preparations. ***Fr.***: Pulviplasmine†; Voxpax.

Helonias

Blazing Star; Chamaelirium; False Unicorn; Helicornio falso; Starwort.

UNII — 4TT3575T88 (Chamaelirium luteum); *DQV54Y5H3U* (Chamaelirium luteum *root*).

Profile

Helonias is the root of *Chamaelirium luteum* (*Helonias dioica*) (Liliaceae). It is used in herbal medicine particularly for gynaecological disorders.

Homoeopathy

Helonias has been used in homoeopathic medicines under the following names: Chamaelirium luteum; Helonias dioica; Helon.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Capsella Complex; Nervatona Calm; Nervatona Focus; ***UK***: Period Pain Relief.

Homoeopathic Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus; ***Austria***: Pascofemin; ***Canad.***: Formula CA 205†; Motherwort Combination 1†; ***Chile***: Calendula Echinacea Comp; Ovukalen; ***Cz.***: Vita C-R15 forte†; Vita C-R15†; ***Fr.***: Diabene; Endhometrol; Helonias Compose; Sativol†; ***Ger.***: Aletris N Oligoplex; Aletris Oligoplex†; Femin-Do; HanoFemin; Infi-China; Naranofem†; Pascofemin; ***Neth.***: Sativol†.

Hemlock

Beaver Poison; Carrot Fern; Ciguë Tachée; Ciguë Tachetée; Conium; Deadly Hemlock; Fool's Parsley; Gefleckter Schierling; Herb Bennet; Kecksies; Kex; Myrkkykatko; Odört; Poison Hemlock; Poison Parsley; Schierling; Spotted Corobane; Spotted Cowbane; Spotted Hemlock; Spotted Parsley; St. Bennett's Herb; Болиголов Пятнистый; Бучиниш.

UNII — Q28R5GF371 (conium); 8N34F5Z76Y (hemlock).

NOTE. Distinguish from Hemlock Spruce (*Tsuga canadensis*, also known as Hemlock), water hemlock (applied to various *Cicuta* spp., notably *Cicuta virosa*, and also to *Oenanthe aquatica*), and hemlock water dropwort (*Oenanthe crocata*, also known as water hemlock). The name Herb Bennet, sometimes applied to hemlock, is more usually used for Avens, *Geum urbanum*. The name Wild Carrot has been applied to Hemlock but usually refers to *Daucus carota* (see p. 2647.2). The name Cicuta has been applied to Hemlock, but belongs to a different genus.

Profile

The fresh or dried leaves and unripe fruit of hemlock, *Conium maculatum* (Apiaceae) have traditionally been used in herbal medicines for their sedative and antispasmodic properties. Hemlock contains the alkaloid coniine, which has actions similar to nicotine (p. 2571.1); poisoning causes paralysis of the peripheral nervous system and skeletal muscles. Death is due to respiratory failure arising from paralysis of the muscles of respiration. All parts of the plant are poisonous, but accidental poisoning with the fresh plant is rare because of its unpleasant odour.

Homoeopathy

Hemlock has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ger.***: Unguentum lymphaticum†; ***Venez.***: Linfoderm.

Homoeopathic Preparations. ***Austria***: Gentos; Lymphdiaral; Memoria; Selenium Med Complex; Vertigoheel; Vertigopas; ***Canad.***: Ginkgo-Compt†; Itires; Tyglan†; ***Chile***: Bioactiv F; Bioactiv V; ***Cz.***: Vertigoheel; ***Fr.***: Adenocynesine†; Conium Complexe No 36†; Dolitravel†; Kalmia Complexe No 18; Sabal Serrulata Compose; Scrofularia Compose; Selenium Complexe No 99; ***Ger.***: Flenin; ISO-Augentropfen C; Lymphaden Complex; Lymphdiaral sensitive N; Lymphdiaral; Lymphdiaral; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Pesendorfer; Prostata-Gastreu N R25; Vertigo Hevert SL; Vertigo-Hevert; Vertigoheel; Vertigopas; Zerosorin SN†; ***Hung.***: Gentos; Vertigoheel; ***Neth.***: Cerebrum comp; Coconium-Gastreu; Dolilite;

Emvita 3; Lymphdiaral; Omnilite; Vertigoheel; *Rus.*: Diet-Comfort (Диет-Комфорт); Gentos (Гентос); Mastopol (Мастопол); Memoria (Меморія); *S.Afr.*: Vertigoheel; *Switz.*: Vertigoheel; *Ukr.*: Gentos (Гентос); Memoria (Меморія); *USA*: Vertigoheel.

Henna

Alheña; Henna Leaf; Henné; Hoja de henna; Lawsonia; Хенна; Хна.
UNII — E5818YZ355.

Profile

Henna is the dried leaves of *Lawsonia inermis* (*L. alba*) (Lythraceae), containing lawsone (p. 2541.2). Powdered henna is used for dyeing the hair, skin, and nails.

Adverse effects. Allergic skin reactions to henna used to dye or temporarily tattoo the skin have been reported but are usually due to additives used to darken the colour and shorten the application time of the dye; allergic reactions to 'plain' henna are rare.[1] The most common cause of reactions is paraphenylenediamine—for further discussion and references, see Hypersensitivity under Paraphenylenediamine, p. 2583.3.

The suggestion that henna may cause neonatal hyperbilirubinaemia is discussed under Lawsone, p. 2541.3.

1. Lestringant GG, *et al.* Cutaneous reactions to henna and associated additives. *Br J Dermatol* 1999; 141: 598–600.

Heptaminol Hydrochloride *(BANM, rINNM)* ⊗

Heptaminol, Chlorhydrate d'; Heptaminol, chlorhydrate de; Heptaminol, hidrocloruro de; Heptaminol hydrochlorid; Heptaminol-hidroklorid; Heptaminolhydrochlorid; Heptaminolhydroklorid; Heptaminoli Hydrochloridum; Heptaminolihydrokloridi; Heptaminolio hidrochloridas; Hidrocloruro de heptaminol; RP-2831; Гептаминола Гидрохлорид.
6-Amino-2-methylheptan-2-ol hydrochloride.
$C_8H_{19}NO,HCl$=181.7
CAS — 372-66-7 (heptaminol); 543-15-7 (heptaminol hydrochloride).
ATC — C01DX08.
ATC Vet — QC01DX08.
UNII — X83RM40HIR.

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

Ph. Eur. 8: (Heptaminol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Profile

Heptaminol hydrochloride is a cardiac stimulant and vasodilator and has been given in the treatment of cardiovascular disorders. Heptaminol and heptaminol adenosine phosphate have also been used.

References.
1. Gharibi L, *et al.* Hair lightening in an hemodialysis patient treated by heptaminol (heptamyl). *Dermatol Online J* 2009; 15: 16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Ampecyclal; Hept-A-Myl; *Indon.*: Hept-A-Myl.

Multi-ingredient Preparations. *Arg.*: Flebitol; *China*: Ginkor Fort (静可福); Cz.: Ginkor Fort; *Fr.*: Debrumyl; Ginkor Fort; *Gr.*: Doprene; *Hong Kong*: Ginkor Fort; *Hung.*: Ginkor Fort†; *Malaysia*: Ginkor Fort; *Port.*: Debrumyl; Forticol; *Rus.*: Ginkor Fort (Гинкор Форт); *Spain*: Denubil; *Thai.*: Ginkor Fort; *Ukr.*: Ginkor Fort (Гинкор Форт).

Herniaria

Bruchkraut; Herba Herniariae; Herniary; Rompepiedras; Rupture-wort; Rupturewort; Грыжник.
UNII — 51O76953TP (Herniaria glabra); E8SAX233E7 (Herniaria glabra flowering).

Profile

Herniaria consists of the dried leaves and flowering tops of various species of rupture-wort, chiefly *Herniaria glabra* and *H. hirsuta* (Caryophyllaceae). It has astringent and diuretic properties and has been given in urinary-tract disorders.

Homoeopathy

Herniaria has been used in homoeopathic medicines under the following names: Herniaria glabra; Hern. gla.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Blasentee St Severin; Uropurat†; Cz.: Urologicka Cajova Smes.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Fr.*: L 8.

Hibiscus

Guinea Sorrel; Hibisci Flos (flowers); Hibisci Sabdariffae Flos (flowers); Hibiscusblüten (flowers); Jamaica Sorrel; Jamaikinių hibiskų žiedai (flowers); Karkadé; Květ. ibišku súdánského (flowers); Oseille de Guinée; Red Sorrel; Rosella; Rosellenkukka (flowers); Rosellhibiskusblomma (flowers); Rozella (flowers); Кислица Ямайская; Гибискус Саблярифа.
UNII — 584J2XT260.

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

Ph. Eur. 8: (Roselle; Hibisci Sabdariffae Flos). The whole or cut dried calyces and epicalyces of *Hibiscus sabdariffa* collected during fruiting.

Profile

Hibiscus is a large genus of flowering plants in the Malvaceae family. The flowers of roselle, *Hibiscus sabdariffa*, are included in herbal preparations for loss of appetite and a range of disorders of the upper respiratory and gastrointestinal tracts.

Culinary uses of *H. sabdariffa* include hibiscus tea, a refreshing caffeine-free beverage made from the flowers.

Homoeopathy

Hibiscus sabdariffa has been used in homoeopathic medicines under the following names: Sabdariffa.

Hibiscus sabdariffa has been used in folk medicine for the treatment of high blood pressure and while recent studies indicate that it might have antihypertensive[1] and hypolipidaemic effects,[2] a systematic review[3] considered that there was no reliable evidence to support its use in hypertension.

1. McKay DL, *et al.* *Hibiscus sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. *J Nutr* 2010; 140: 298–303.
2. Mozaffari-Khosravi H, *et al.* Effects of sour tea (*Hibiscus sabdariffa*) on lipid profile and lipoproteins in patients with type II diabetes. *J Altern Complement Med* 2009; 15: 899–903.
3. Wahabi HA, *et al.* The effectiveness of *Hibiscus sabdariffa* in the treatment of hypertension: a systematic review. *Phytomedicine* 2010; 17: 83–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ukr.*: Aflazin (Афлазин).

Multi-ingredient Preparations. *Fr.*: Hydracur; *Hung.*: Telma; *USA*: Cardiopress.

Histamine

Histamiini; Histamin; Histamina; Histaminum; Гистамин.
2-(Imidazol-4-yl)ethylamine.
$C_5H_9N_3$=111.1
CAS — 51-45-6.
ATC — V04CG03.
ATC Vet — QV04CG03.
UNII — 820484N8I3.

Histamine Hydrochloride

Dihidrocloruro de histamina; Histamiinidihydrokloridi; Histamina, hidrocloruro de; Histamin-dihydrochlorid; Histamindihydrochlorid; Histamindihydroklorid; Histamine, dichlorhydrate d'; Histamine Dihydrochloride (USAN); Histamini Dihydrochloridum; Histamino dihidrochloridas; Histaminy dichlorowodorek; Hisztamin-dihidroklorid; Гистамина Гидрохлорид.
$C_5H_9N_3,2HCl$=184.1
CAS — 56-92-8.
ATC — L03AX14; V04CG03.
ATC Vet — QL03AX14; QV04CG03.
UNII — 3POA0Q644U.

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

Ph. Eur. 8: (Histamine Dihydrochloride). Hygroscopic, colourless crystals or white or almost white crystalline powder. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 2.85 to 3.60. Protect from light.

Histamine Phosphate

Difosfato de histamina; Histamiinifosfaatti; Histamin difosfát monohydrát; Histamina, fosfato de; Histamine Acid Phosphate; Histamine Diphosphate; Histamine, phosphate d'; Histaminfosfat; Histamini Diphosphas Monohydricus; Histamini phosphas; Histamino fosfatas; Histaminphosphat; Histaminy fosforan; Hisztamin-foszfát; Гистамина Фосфат.
$C_5H_9N_3,2H_3PO_4,H_2O$=325.2
CAS — 51-74-1 (anhydrous histamine phosphate).
ATC — V04CG03.
ATC Vet — QV04CG03.
UNII — QWB37T4WZZ.

Pharmacopoeias. *Chin.* and *US* specify the anhydrous substance.

USP 36: (Histamine Phosphate). Anhydrous histamine phosphate occurs as colourless, odourless, long prismatic crystals. Is stable in air but is affected by light. Soluble 1 in 4 of water. Its solutions are acid to litmus. Store in airtight containers. Protect from light.

Stability. A study concluded that solutions of histamine phosphate could be sterilised by heating in an autoclave with little degradation.[1] Autoclaved solutions could be stored for a minimum of 4 months.

1. McDonald C, *et al.* Stability of solutions of histamine acid phosphate after sterilization by heating in an autoclave. *J Clin Pharm Ther* 1990; 15: 41–4.

Uses and Administration

Histamine causes stimulation of smooth muscle, especially of the bronchioles, and lowers blood pressure by dilating the arterioles and capillaries. It also stimulates exocrine gland secretion, especially the gastric glands.

Intradermal injection of histamine produces the characteristic 'triple response' of erythema, flare, and wheal. This is used as a control response in skin testing for hypersensitivity. Also, since it is mediated in part by axon reflexes, it has been used to test the integrity of sensory nerves, for example in leprosy.

Inhalation of histamine causes bronchoconstriction and is used as a test of bronchial reactivity.

Histamine has also been given subcutaneously to identify the causes of achlorhydria and intravenously in the diagnosis of phaeochromocytoma, but safer tests are generally preferred.

Histamine is included in some combination topical preparations for musculoskeletal disorders.

Histamine hydrochloride is given subcutaneously as adjunctive treatment with interleukin-2 to patients with acute myeloid leukaemia in first remission after consolidation therapy—see p. 810.3 for further details including doses. Histamine hydrochloride has also been tried as an adjunct to interferons and other drugs in the management of hepatitis C.

Adverse Effects, Treatment, and Precautions

Injection of histamine salts can produce adverse effects including headache, fatigue, pyrexia, dizziness, flushing of the skin, general vasodilatation with a fall in blood pressure, tachycardia, bronchial constriction and dyspnoea, visual disturbances, vomiting, diarrhoea, and other gastrointestinal effects. These reactions can be severe; excessive dosage can produce collapse and shock, and may be fatal. Reactions may occur at the injection site.

Some of these effects may be relieved by an antihistamine, but adrenaline may be required and should always be available.

Histamine salts should be used with care in patients with asthma or other hypersensitivity disorders, in elderly patients, and in patients with cardiovascular disorders. Histamine salts should also be given with caution to patients with severe renal impairment because they may be more sensitive to the blood pressure lowering effects of histamine. Adverse effects such as dizziness and blurred vision may affect the patient's ability to drive or operate machinery after receiving histamine salts.

Interactions

The performance of histamine skin tests can be altered by co-administration of some drugs. Response to histamine is suppressed by antihistamines and can last from 1 to 40 days depending on the antihistamine. Tricyclic antidepressants decrease skin reactivity to histamine that may last for several weeks. Intravenous infusion of dopamine has also been reported to inhibit the histamine skin test response. There is the theoretical possibility that oral terbutaline and parenteral ephedrine might reduce the histamine skin test response since they have been shown to decrease allergen-induced wheal. Conversely the histamine skin test response can be significantly increased by propranolol.

Patients receiving histamine hydrochloride as adjunctive treatment with interleukin-2 for acute myeloid leukaemia (see p. 810.3) should not be given histamine H_2-antagonists such as cimetidine that have imidazole structures similar to histamine, systemic corticosteroids, or clonidine. Drugs that should be avoided or used with caution with exogenous histamine include antihistamines, as well as antipsychotics

that have histamine H_1-antagonist activity, and antidepressants, which may have histamine H_1- and H_2-antagonist activity. Concurrent administration of antihypertensive drugs, including beta blockers, increases the toxicity of exogenous histamine and the combination should be used with caution or avoided. MAOIs, antimalarials, and antitrypanosomal drugs may alter the metabolism of exogenous histamine and should also be used with caution or avoided. Endogenous histamine may be released by neuromuscular blockers, opioid analgesics, and some contrast media, which should be taken into consideration if histamine is given exogenously to patients before undergoing surgical or diagnostic procedures.

Pharmacokinetics

Histamine salts exert a rapid, though transient, effect when given parenterally. Histamine is rapidly metabolised by methylation and oxidation; the metabolites are excreted in the urine.

References.
1. Middleton M, *et al.* Pharmacokinetics of histamine dihydrochloride in healthy volunteers and cancer patients: implications for combined immunotherapy with interleukin-2. *J Clin Pharmacol* 2002; 42: 774–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Histatrol; *Cz.*: Ceplene; *Ger.*: Ceplene; *Irl.*: Ceplene; *Mex.*: Destamin; *Neth.*: Ceplene; Soluprick Controlevloeistoffen; *Norw.*: Ceplene; *Pol.*: Ceplene; *Port.*: Ceplene; Soluprick; *Swed.*: Ceplene; *UK*: Ceplene; *USA*: Histatrol.

Multi-ingredient Preparations. *Arg.*: Histaglobin; *Austria*: Histaglobin†; *Fr.*: Algipan†; *India*: Algipan; Histaglobulin; *Neth.*: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; *Pol.*: Histaglobulina; *S.Afr.*: Histaglobin†; Infrarub†; *Switz.*: Radalgin†.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Snore Eze; Snorestop; *Canad.*: Adrisin†; Hepar Compositum; Homeodel 15†; Luffeel Nasal Spray; Sabalia; Snore Stop; *Chile*: Apis Compuesto; Similibus; *Cz.*: Luffeel; Rhinallergy; *Fr.*: Dolistamine†; Polyrhinium; Rhinallergy; *Ger.*: Hepar comp; Luffeel Comp; *Hung.*: Luffeel; *Neth.*: Homeocare Allerlo; Luffeel H; Prurilite; Snurdim; Urtizon complex; *Switz.*: Polyrhinium; Rhinallergy.

Pharmacopoeial Preparations
USP 36: Histamine Phosphate Injection.

Histoplasmin

Histoplasmina; Гистоплазмин.
CAS — 9008-05-3.

Profile

Histoplasmin contains standardised culture filtrates of the fungus *Histoplasma capsulatum*. It has been given intradermally as an aid to the diagnosis of histoplasmosis. However, the diagnostic value of the test has been questioned and it may interfere with serological tests for histoplasmosis.

Histoplasmin has also been used, in conjunction with other antigens, to assess cell-mediated immunity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Histolyn-CYL†.

Homocysteine Thiolactone Hydrochloride

3-Aminodihydro-2(3*H*)-thiophenone hydrochloride.
C_4H_8ClNOS=153.6
CAS — 10593-85-8 (homocysteine thiolactone); 3622-59-1 (homocysteine thiolactone hydrochloride).

Profile

Homocysteine thiolactone has been used in preparations for the treatment of liver disorders. Its hydrochloride salt has been used as a mucolytic. Homocysteine thiolactone is a metabolite of homocysteine and has been implicated in the pathogenesis of some cardiovascular diseases (see p. 2063.3).

References.
1. Chwatko G, Jakubowski H. Urinary excretion of homocysteine-thiolactone in humans. *Clin Chem* 2005; 51: 408–15.
2. Jakubowski H. The molecular basis of homocysteine thiolactone-mediated vascular disease. *Clin Chem Lab Med* 2007; 45: 1704–16.

Horseradish

Armoracia; Meerrettich; Rábano picante; Rábano rusticano; Raifort; Хрен.
UNII — 8DS6G120HJ.

Profile

Horseradish, the root of *Cochlearia armoracia* (*Armoracia rusticana; Nasturtium armoracia; Radicula armoracia*) (Cruciferae), has diuretic and antiseptic properties and stimulates the digestion. It is used in gastrointestinal, respiratory-tract, and urinary-tract disorders, and has also been used externally.

Horseradish is widely used as a food flavouring and condiment.

Homoeopathy

Horseradish has been used in homoeopathic medicines under the following names: Cochlearia armoracia; Cochlearia arm; Coch. ar.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Garlic and Horseradish + C Complex†; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Cough, Cold & Flu Day + Night; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; Super Strength Horseradish Garlic + C; Ultra Allergy Defense; *Ger.*: Angocin Anti-Infekt N; *Switz.*: Kernosan Elixir; Sanogencive; *UK*: Mixed Vegetable Tablets.

Homoeopathic Preparations. *Austria*: Asinis; *Fr.*: Poconeol no 34; *Port.*: Homeodent†; *Rus.*: Asinis (Асинис); *Ukr.*: Asinis (Асинис).

Hyaluronic Acid *(BAN)*

Hialurónico, ácido; Гиалуроновая Кислота.
(1→3)-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-*O*-β-D-glucopyranosiduronan.
CAS — 9004-61-9.
ATC — D03AX05; M09AX01; R01AX09; S01KA01.
ATC Vet — QD03AX05; QM09AX01; QR01AX09; QS01KA01.

NOTE. The term Hyaluronan is used to cover both hyaluronic acid and sodium hyaluronate.

Sodium Hyaluronate *(BANM)*

Hialuronato sódico; Hyaluronate Sodium (USAN); Natrii Hyaluronas; Natrio hialuronatas; Nátrium-hialuronát; Natriumhyaluronaatti; Natriumhyaluronat; Natrium-hyaluronát; NRD-101; Sodium, hyaluronate de; Sodyum Hiyalüronat; Гиалуронат Натрия.
CAS — 9067-32-7.
ATC — D03AX05; M09AX01; S01KA01.
ATC Vet — QD03AX05; QM09AX01; QS01KA01.
UNII — YSE9PPT4TH.

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

Ph. Eur. 8: (Sodium Hyaluronate). The sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units. It is extracted from cocks' combs or obtained by fermentation from streptococci (Lancefield Groups A and C). A white or almost white, very hygroscopic powder or a fibrous aggregate. Sparingly soluble to soluble in water; practically insoluble in dehydrated alcohol and in acetone. A 0.5% solution in water has a pH of 5.0 to 8.5. Store in airtight containers. Protect from light and humidity.

Uses and Administration

Hyaluronic acid is widely distributed in body tissues and intracellular fluids, including the aqueous and vitreous humour, and synovial fluid; it is a component of the ground substance or tissue cement surrounding cells.

A viscous solution of sodium hyaluronate is used during surgical procedures on the eye, for example for cataract extraction. Introduction of the solution into the anterior or posterior chamber via a fine cannula or needle allows tissues to be separated during surgery and protects them from trauma. Sodium hyaluronate eye drops 0.1% are also used for the relief of dry eye and as a contact lens lubricant.

Sodium hyaluronate is given by intra-articular injection in the treatment of osteoarthritis of the knee. Doses vary according to the preparation used, but are of the order of 20 to 25 mg once weekly for 5 weeks or up to 30 mg once weekly for 3 or 4 weeks; it is generally recommended that the treatment course for any individual joint should not be repeated within 6 months. Sodium hyaluronate is also used during arthroscopic procedures to flush out irrigating solutions and act as a temporary substitute for synovial fluid.

Hyaluronic acid is applied topically to promote wound healing. Zinc hyaluronate has also been used. A film containing sodium hyaluronate and carmellose is used to prevent surgical adhesion. Sodium hyaluronate has also been used in the management of lesions of the oral mucosa.

Hylans, which are polymers derived from hyaluronic acid, are used similarly for osteoarthritis and wound care.

Sodium hyaluronate instilled intravesically has been used as a temporary replacement of the glycosaminoglycan layer in the bladder for the symptomatic treatment of interstitial cystitis.

Topical formulations of diclofenac in hyaluronic acid (CT-1101, AT-2101) are used in the treatment of actinic keratoses (but distinguish from an oral formulation of afegostat tartrate (p. 2432.1) under investigation for use in Gaucher disease that also carries the code AT-2101).

Hyaluronic acid has been used as a dermal filler for the correction of moderate to severe facial wrinkles and folds (see Photoageing, p. 1686.2).

Reviews.
1. Goa KL, Benfield P. Hyaluronic acid: a review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994; 47: 536–66.
2. Adams ME, *et al.* A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Safety* 2000; 23: 115–30.

Actinic keratoses. For references to the use of diclofenac in a hyaluronic acid gel in the treatment of actinic keratoses, see p. 49.2.

Dry eye. The usual management of dry eye (p. 2190.1) is with artificial tears. Sodium hyaluronate has also been reported to be of some benefit. Alleviation of symptoms[1-3] and an increase in tear film stability[1,2] has been shown after topical application of sodium hyaluronate solution (0.1 or 0.2%) compared with saline-based placebo solutions. However, another study[4] failed to show any advantage over placebo, although it has been suggested[4,5] that sodium hyaluronate might play a role in maintaining a healthy corneal epithelium.

1. Mengher LS, *et al.* Effect of sodium hyaluronate (0.1%) on break-up time (NIBUT) in patients with dry eyes. *Br J Ophthalmol* 1986; 70: 442–7.
2. Sand BB, *et al.* Sodium hyaluronate in the treatment of keratoconjunctivitis sicca: a double masked clinical trial. *Acta Ophthalmol (Copenh)* 1989; 67: 181–3.
3. Condon PI, *et al.* Double blind, randomised, placebo controlled, crossover, multicentre study to determine the efficacy of a 0.1% (w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. *Br J Ophthalmol* 1999; 83: 1121–4.
4. Shimmura S, *et al.* Sodium hyaluronate eyedrops in the treatment of dry eyes. *Br J Ophthalmol* 1995; 79: 1007–11.
5. Aragona P, *et al.* Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br J Ophthalmol* 2002; 86: 181–4.

Osteoarthritis. In osteoarthritis, the size and concentration of hyaluronic acid molecules naturally present in synovial fluid is reduced. Thus, one approach in the management of osteoarthritis (p. 12.3) of the knee is viscosupplementation of the synovial fluid by the intra-articular injection of hyaluronic acid or its derivatives. Such injections may reduce pain over 1 to 6 months but may be associated with a short-term increase in knee inflammation; there is some suggestion that any benefit is longer lasting than with intra-articular corticosteroids. Some studies suggest that viscosupplementation may be an effective option for patients who are unable to take oral NSAIDs or have regular intra-articular corticosteroids, and who are unsuitable candidates for joint replacement surgery, although there appears to be considerable variability in clinical response between products, as well as in the variables being assessed and length of treatment.

References.
1. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. *J Rheumatol* 1998; 25: 2203–12. Correction. *Ibid.* 1999; 26: 1216.
2. Anonymous. Hyaluronan or hylans for knee osteoarthritis? *Drug Ther Bull* 1999; 37: 71–2.
3. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; 38: 602–7.
4. Wobig M, *et al.* The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther* 1999; 21: 1549–62.
5. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med* 2002; 162: 245–7.
6. Lo GH, *et al.* Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; 290: 3115–21.
7. Bellamy N, *et al.* Viscosupplementation for the treatment of osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 09/05/06).

Wound healing. Hyaluronic acid has been used to aid wound healing,[1,2] the overall management of which is discussed on p. 1690.1.

1. Soldati D, *et al.* Mucosal wound healing after nasal surgery: a controlled clinical trial on the efficacy of hyaluronic acid containing cream. *Drugs Exp Clin Res* 1999; 25: 253–61.
2. Harris PA, *et al.* Use of hyaluronic acid and cultured autologous keratinocytes and fibroblasts in extensive burns. *Lancet* 1999; 353: 35–6.

Adverse Effects

There have been reports of a transient rise in intra-ocular pressure when sodium hyaluronate was given into the eye. When injected into the knee, pain and inflammation may

occur at the injection site. There have also been occasional reports of hypersensitivity, including, rarely, anaphylaxis.

Effects on the eyes. Crystalline deposits on intra-ocular lenses have been reported in patients after use of a high viscosity sodium hyaluronate preparation during cataract surgery.[1]

1. Jensen MK, *et al.* Crystallization on intraocular lens surfaces associated with the use of Healon GV. *Arch Ophthalmol* 1994; 112: 1037–42.

Effects on the skin. A cutaneous granulomatous reaction has been reported in a woman 5 weeks after treatment with synthetic hyaluronic acid for cosmetic use as a dermal filler.[1] All cutaneous lesions resolved spontaneously within 3 months without scarring.

1. Ghislanzoni M, *et al.* Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br J Dermatol* 2006; 154: 755–8.

Inflammatory reaction. Severe peritoneal inflammation has been reported[1] after use of a sodium hyaluronate-based bioresorbable membrane to prevent postoperative adhesion formation.

1. Klingler PJ, *et al.* Seprafilm-induced peritoneal inflammation: a previously unknown complication: report of a case. *Dis Colon Rectum* 1999; 42: 1639–43.

Precautions

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hyaluronic acid given by injection for the treatment of musculoskeletal 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 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acuaiss; Aquify; Artflex; Cystistat; Dropstar; Gengigel; Hialudorf; Hyabak; Hyalart; Hyalofill-F; Hyalomb; Hyasol; Iuronicoderm; Maxiostenil; Miniostenil; Osmolagrimas; Provisc†; Synvisc; Viscoderm; ***Austral.***: AMO Vitrax†; Healon; Luxyal; Ophthalin†; Provisc; Synvisc; ***Austria***: Artzal; Bionect; Hyalgan; ***Belg.***: Gengigel; Hyalgan; ***Braz.***: Densitium; Fermathron; Healon†; Hyaludermin; Polireumin; Suplasyn; Suprahyal; Synvisc; ***Canad.***: Cystistat; Durolane; Hyalgan; Monovisc; NeoVisc; Orthovisc; Suplasyn; Synvisc; ***Chile***: Biolon; Bucerin Emulsion†; Healon†; Hyalgan; Hylaform†; Lagricel Ofteno; Neolucid Ultra HR; Suprahyal; Synvisc; Toptear; ***China***: ARTZ (阿尔治); Hialid (爱丽); Hyal (哈艾路); Iviz (爱维); Runjie (润洁); Shipeike (施沛克); Soiast (施沛特); ***Cz.***: Hyalgan; ***Denm.***: Artz; Hyalgan; ***Fin.***: Artzal; Hyalgan; ***Fr.***: Adant; Aftamed; Amvisc†; Arthrum H; Biovisc†; Coxarthrum; Durolane; Effidia†; Euflexxa; Go-On; Hyabak; Hyalgan; Hyaline; Hyalugel; Hyaluzinc; Hylo-COMOD; Hylovis; Ialuset; Idune; Ostenil; Oxens; Provisc; Sinovial; Structovial; Succeev; Suplasyn†; Synocrom; Synvisc; Vitrax†; ***Ger.***: Artelac Splash; Artroject; Biolan; Biolon†; Curavisc; Cystistat†; Endogel; Fermathron; Gelbag; Genteal HA; Go-On; Hy-GAG; Hyaject; Hya-Ophtal; Hyabak; Hyalart; Hyalubrix; Hyaluron†; Hylan; Hylo-COMOD; Hylo-Gel; Hylo-Lasop; Hylo-Parin; Hylo-Vision; Hysan; Laservis; Monovisc; Orthovisc; Ostenil; Oxyal; Provisc; Recosyn; Sinovial; Suplasyn†; Synvisc; TwinVisc; Uni-Injekt; Unike; Viscoseal; Visiol; Vislube; Vismed; VisThesia; Xidan EDO; ***Gr.***: Arthryal; Biolon; Gonilert; Healon; Hyalart; Provisc; Viscure; Yardel; ***Hong Kong***: Artelac Advanced; Connettivina; Go-On; Healon†; Hialid; Hyalgan; Hyruan; Jonexa; Synocrom; Synvisc; Vismed; ***Hung.***: Curiosin; Hyalgan; ***India***: Fain; Halonix; Healon; Hymoist; Hyopt; Hyvisc; LG Hyal; LG Hyruan; Synvisc; Visial; ***Indon.***: Adant; Bionect; Cytistat; Durolane; Hialid; Hyalgan; Hyaloph; Lydium; Osflex; Sanorine; Suplasyn; ***Irl.***: Hyalgan; Suplasyn†; ***Israel***: Adant†; Arthrease; Biolon; Curavisc; Eyecon; Healon; Hylo-COMOD; Hysan; Orthovisc†; Suplasyn; Synvisc; ***Ital.***: Artelac Advanced; Artz; Cicatridina; Connettivina; Dropstar; Durolane; Fillast; Go-On; Hy-Drop; Hyabak; Hyalart; Hyalgan; Hyalistil; Hyalofill-F; Hyalubrix; Hylo-COMOD; Hyluprotect; Ial; Ialoclean; Ialum; Ialurex; Irilens; Jaloskin; Oftaial; Opisial†; Oxyal; Provisc; Rugantil†; Skin-B†; Skin-R†; Synocrom; Synvisc; Vismed; ***Jpn***: Hyalein; Suvenyl; Synvisc; ***Malaysia***: Adant; Aftamed; Curiosin; Gengigel; Go-On; Hyal; Hyalgan; Hylo-COMOD; Hyruan; Jointmax; Provisc†; Sinovial; Suplasyn; Synvisc; Viscoseal; Visiol; Vislube†; Vismed; ***Mex.***: Biolon; Dropstar; Eyestil; Hyasol; Lagricel; Suprahyal; Synvisc; Zonaker; ***Mon.***: Oxyal†; ***NZ***: Healon; Hyalgan; Hylaform; Juvederm; Ophthalin†; Provisc; Restylane; Synvisc; ***Philipp.***: Curiosin; Go-On; Hialid; Provisc; Synove; ***Pol.***: Hyalgan; Synvisc; ***Port.***: Artz; Hyalart; ***Rus.***: Curiosin (Куриозин); Healon (Хеалон); Hyalgan (Гиалган); Hylo-COMOD (Хило-КОМОД); Hylomax-COMOD (Хиломакс-КОМОД); ***S. Afr.***: AMO Vitrax†; Biolon†; Biolone; Healon; Microvisc; Provisc; Suplasyn; ***Singapore***: Curiosin; Cystistat†; Go-On; Hialid; Hyalgan; Hylaform†; Juvederm; Monovisc; Orthovisc; Provisc†; Sanorine; Suplasyn; Synvisc; Vislube†; Vismed; ***Spain***: Hyabak†; Hyalart; Hyalgan; ***Swed.***: Artzal; Hyalgan; Synvisc; ***Switz.***: Fermavisc; Hyalur; HycoSan5; Hylo-COMOD; Hylo-Gel; Hysan†; Ial; Ialugen; Laservis; Ostenil; Rhinogen; Sinovial; Suplasyn; Synvisc†; Viscoseal; Visiol; Vislube; Vismed; ***Thai.***: Adant; Go-On; Hialid; Hyalgan; Hyruan; Ial; Juvederm Ultra XC; Ophthalin†; Provisc; Suplasyn; Synvisc; Vislube; ***Turk.***: Adant; Amvisc; Biolon; Healon; Hyalgan; Ial†; Ophtalin Plus†; Orthovisc; Ostenil; Provisc†; Synvisc; ***UK***: Arthrease; Clinitas; Cystistat; Euflexxa; Fermathron; Gengigel; Hyabak; Hyalgan; Hyalofill; Hycosan; Hylo-Forte; Hylo-Tear; Lubristil; Lumecare Extra Gentle; Ocusan; Ophthalin; Optrex Contact Lens Friendly Eye Drops; Orthovisc; Ostenil; Oxyal; Suplasyn; Synocrom; Synvisc; Viscoseal; Vismed; ***Ukr.***: Curiosin (Куриозин); Hyaral (Гиаral); Kuriosin (Куриозин); Synhyal (Синхиал); ***USA***: AMO Vitrax†; Amvisc; Bionect; Coease; Euflexxa; Healon; Hyalgan; HyGel; Hylaform†; Hylase; Hylira; Juvederm; Orthovisc; Perlane; ProVisc; Restylane; Shellgel; Supartz; Synvisc; ***Venez.***: Hyalgan; Lagricel Ofteno; Suprahyal; Synvisc; Toptear.

Multi-ingredient Preparations. ***Arg.***: Alosol; Blink Contacts; Cellskinlab Hydragel B5; Culuflex H†; Epitheliale AH; Estri-Atlas; Fusimed; Hyalcrom NF; Hyalcrom; Hyalogran; Hyalomatrix-PA; Hydratone; Ingebrax†; Iuronico Biotic; Lacrimax†; Maxilac†; Maxus; Muvar; Natura Confort; Neoprost; Ocusun; Panoxi; Revi-Atlas; Vera Plus; Viscoat†; Vita-C Derms's; Yusin Tears II; ***Austral.***: Atopiclair†; Blink Contacts; Duovisc; Viscoat†; ***Belg.***: Physiologica Nasal; ***Braz.***: Seprafilm; ***Chile***: Epithelial AH; Estri-Atlas; Gelclair; Hyaluron; Hydragel B5 CKL; Hydraphase Ojos; Hydrating B5 Gel†; Redermic Piel; Redermic XL; Revi-Atlas; Ureadin Rx RD; ***China***: CP Bright (正大维他); Frecoseryl (润尔乐); Fredex (科恒); Run Jie (润洁); ***Cz.***: Ialugen Plus; ***Fr.***: Bactigyn; Cicaplast; Cicatridine; Cicatridine; Flexi-max; Ialuset Plus; Ilast Care; Ilast Hydra; Ilast O'Clean; Ilast Post-Op; Mucogyne; Mycoress; Navitae; Saugella Antiseptic; Saugella Dermoliquide; Saugella douceur Poligyn; Urgo Cicatrices; Veganix; Viscoat†; Vitrecor; ***Ger.***: Allamare; Bepanthen Augentropfen; DisCoVisc; Duovisc; Gelclair; Herba-Vision Augenbad; Herba-Vision Augentrost; Herba-Vision Blaubeere; Hya-ject Plus; Hylo-Care; Hylo-Vision HD Plus; Ialunara; Ilast Care; Trium; Viscoat; ***Gr.***: Viscoat; ***Hung.***: Ialugen Plus; ***Indon.***: Aloclair; Atopiclair; Vitadrop; ***Israel***: Aphtagone†; Aptha-X†; Atopiclair; Salinagel; Xclair; ***Ital.***: Altergen; Biolastic T5; Cartijoint†; Connettivina Plus; DisCoVisc†; Dropyal; Hyalogran; Hyalosilver; Hylo-Care; Idroskin C; Lesiorepar; Migel; Naset; Osmogel; Respifree; Resvelife; Sirmiogel; Trofo 5; Ulcedar; Vaginol; Viscoat; Xanternet; ***Malaysia***: Aloclair; Aqua Care; Duovisc†; Hyiodine; Prelactic; Seprafilm; Viscoat†; Vitadrop; ***Mex.***: Cetopic; Emolin Neo; Grimal; Humylub Ofteno; Hyalcrom NF; Hyalox; ***Mon.***: Monasens; ***NZ***: Viscoat; ***Philipp.***: Viscoat; ***Port.***: Synchrorose Intensivo; Synchrovit; ***Rus.***: Hyaferone (Гиаферон); Hylozar-COMOD (Хилозар-КОМОД); ***S.Afr.***: Duovisc†; Viscoat; ***Singapore***: Atopiclair; BCC; Duovisc; RejuvaSkin Anti-Aging Serum; Scar Esthetique; Seprafilm; Viscoat†; ***Switz.***: Alphastria; Hylo-Care; Ialugen Plus; Lacrycon; Nasmer 3plus; Nasmer free; ***Thai.***: DisCoVisc; Duovisc; Viscoat; ***Turk.***: Duovisc†; Viscoat; ***UK***: Artelac Rebalance; Atopiclair; Blink Intensive Tears; Gelclair; Hylo-Care; Rohto Dry Eye Relief; Seprafilm; Xclair; Zuidex; ***Ukr.***: Curiosin (Куриозин); Kuriosin (Куриозин); ***USA***: Atopiclair; Deflux; DisCoVisc; Gelclair; Healon Yellow†; Miaderm Radiation Relief; Ocean Nasal Moisturizer; RadiaPlex Rx; Seprafilm; Solesta; Viscoat; Zacare Kit; ***Venez.***: Cepin; Epitheliale AH.

Hyaluronidase *(BAN, rINN)*

Hialuronidasa; Hialuronidaze; Hialuronidāz; Hiyalūronidaz; Hyaluronidaasi; Hyaluronidas; Hyaluronidasa; Hyaluronidasum; Гиалуронидаза.

CAS — 9001-54-1.

ATC — B06AA03.

ATC Vet — QB06AA03.

UNII — 8KOG53Z5EM (bovine hyaluronidase); 64R4OHP8T0 (ovine hyaluronidase).

NOTE. The name Kinetin (p. 1710.2) has also been used as a proprietary name for hyaluronidase.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). *US* includes as an injectable form.

Ph. Eur. 8: (Hyaluronidase). An enzyme capable of hydrolysing mucopolysaccharides of the hyaluronic acid type. It is prepared from the testes of mammals by a method that has been shown to reduce contamination by known infectious agents to acceptable limits; a suitable stabilising agent may be added to the purified preparation. A white or yellowish-white, amorphous powder; it contains not less than 300 international units of hyaluronidase activity per mg, calculated with reference to the dried substance. Soluble in water; practically insoluble in alcohol and in acetone. A 0.3% solution in water has a pH of 4.5 to 7.5. Store at 2 degrees to 8 degrees in airtight containers.

Units

The international and USP units are equivalent. One international or USP unit is equivalent to one turbidity-reducing unit or about 3.3 viscosity-reducing units.

Uses and Administration

Hyaluronidase is an enzyme that reversibly depolymerises hyaluronic acid (p. 2526.2), a component of the ground substance or tissue cement surrounding cells, thereby temporarily reducing its viscosity and rendering the tissues more readily permeable to injected fluids.

Hyaluronidase is used to increase the speed of absorption and reduce discomfort due to subcutaneous or intramuscular injection of fluids, to promote resorption of excess fluids and extravasated blood in the tissues, and to increase the efficacy of local anaesthesia.

In the UK, the usual dose as an adjunct to subcutaneous or intramuscular injection is 1500 units, added directly to the injection. To aid the dispersal of extravasated fluids or blood, the same dose is given in 1 mL of Water for Injections or 0.9% sodium chloride into the affected area. Lower doses of hyaluronidase are used in some countries; in the USA, the usual dose is 150 units.

In hypodermoclysis, hyaluronidase is used to aid the subcutaneous administration of relatively large volumes of fluids, especially in infants and young children, where intravenous injection is difficult. Care should be taken in the treatment of children and the elderly to control the speed and total volume given and to avoid overhydration. Hyaluronidase may be added to the injection fluid or may be injected into the site before the fluid is given. In the UK, 1500 units of hyaluronidase is generally given with each 500 to 1000 mL of fluid for subcutaneous use, but in the USA, 150 units of hyaluronidase is considered adequate for each litre of hypodermoclysis solution.

In the UK, the diffusion of local anaesthetics is accelerated by the addition of 1500 units of hyaluronidase to the anaesthetic solution. It has also been used in ophthalmology as an aid to local anaesthesia at recommended doses of 15 units/mL of local anaesthetic solution. Hyaluronidase has also been used for the treatment of vitreous haemorrhage and diabetic retinopathy.

To improve the resorption of radiopaque agents in subcutaneous urography, hyaluronidase is injected subcutaneously in a dose of 75 units over each scapula followed by injection of the contrast medium at the same site.

Recombinant human hyaluronidase is used for the preparation of oocytes during IVF.

Hyalosidase (GL enzyme) is a highly purified form of hyaluronidase that has been studied.

General references.

1. Etesse B, *et al.* Hyaluronidase: plaidoyer pour un retour. *Ann Fr Anesth Reanim* 2009; 28: 658–65.
2. Dunn AL, *et al.* Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management. *Expert Opin Biol Ther* 2010; 10: 127–31.

Ophthalmic surgery. In a study[1] involving 150 consecutive patients undergoing surgery for senile cataract, retrobulbar anaesthesia with lidocaine 2% solution plus adrenaline 1:100 000 and hyaluronidase 15 units/mL produced successful anaesthesia in 69 of 75 cases (92%), which was significantly better than 42 of 75 treated with lidocaine plus adrenaline alone. Although poor results have been reported from hyaluronidase and a local anaesthetic without adrenaline to restrict local anaesthetic absorption, the use of the enzyme and adrenaline was recommended as an aid to achieving complete ocular akinesia and anaesthesia in cataract surgery. Hyaluronidase has also been used with a mixture of bupivacaine and lidocaine for peribulbar anaesthesia, but results have been conflicting. In a study[2] in 50 patients, addition of hyaluronidase 25 units/mL of local anaesthetic mixture had no significant effect on time to satisfactory anaesthesia. However, in a second study[3] involving 200 patients, addition of hyaluronidase 50 or 300 units/mL improved the quality of the peribulbar block and, in the case of the higher concentration, also increased the speed of onset.

1. Thomson I. Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract. *Br J Ophthalmol* 1988; 72: 700–2.
2. Prosser DP, *et al.* Re-evaluation of hyaluronidase in peribulbar anaesthesia. *Br J Ophthalmol* 1996; 80: 827–30.
3. Dempsey GA, *et al.* Hyaluronidase and peribulbar block. *Br J Anaesth* 1997; 78: 671–4.

Adverse Effects and Precautions

Sensitivity to hyaluronidase occasionally occurs. Because of the danger of spreading infection, the enzyme generally should not be injected into or around an infected area. It has been suggested that the presence of malignancy may similarly be a contra-indication to the use of hyaluronidase. It should not be given by intravenous injection nor should it be used for anaesthetic procedures in cases of unexplained premature labour. Hyaluronidase should not be applied directly to the cornea. It should not be used to reduce the swelling of bites or stings.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Unidasa; ***Austral.***: Hyalase; ***Austria***: Hylase; ***Braz.***: Hyalozima; ***Cz.***: Hylase; ***Ger.***: Hylase; ***Gr.***: Hyalase; ***Hong Kong***: Hyalase†; ***India***: Facidase; Hylorase;

Hynidase; *Irl.*: Hyalase; *Israel*: Hyalase; *Neth.*: Hyason; *NZ*: Hyalase; *Rus.*: Longidaza (Лонгидаза); Lydase (Лидаза); Lyrase (Лираза); Nydase (Нидаза); *S.Afr.*: Hyalase†; *Singapore*: Hyalase; *UK*: Hyalase; *USA*: Amphadase; Hydase†; Hylenex; Vitrase.

Multi-ingredient Preparations. *Arg.*: Nilflux; *Braz.*: Oto-Xilodase; Postec; Xilodase; *Gr.*: Lasonil; *Ital.*: Lido-Hyal; *Pol.*: Helason; *Switz.*: Lido-Hyal†.

Pharmacopoeial Preparations
BP 2014: Hyaluronidase Injection;
USP 36: Hyaluronidase for Injection; Hyaluronidase Injection.

Hydrangea

Hidrangea; Raíz de hortensia; Seven Barks; Smooth Hydrangea; Wild Hydrangea; Гортензия.
UNII — Z82ZU9MJ6M (Hydrangea arborescens); MRX3W33KCB (Hydrangea arborescens bark); SFK828Q2DE (Hydrangea arborescens root).

Profile

Hydrangea, the root of *Hydrangea arborescens* (Hydrangeaceae), has diuretic and litholytic properties and is used for genito-urinary disorders including renal and urinary calculi.

Homoeopathy

Hydrangea has been used in homoeopathic medicines under the following names: Hydrangea arborescens; Hydrang.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Antiglan; Backache.

Homoeopathic Preparations. *Ger.*: Pascosabal.

Hydrastine Hydrochloride

Hidrastina, hidrocloruro de; Hydrastyny chlorowodorek; Гидрастина Гидрохлорид.
6,7-Dimethoxy-3-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one hydrochloride.
$C_{21}H_{21}NO_6.HCl$=419.9
CAS — 118-08-1 (hydrastine); 5936-28-7 (hydrastine hydrochloride).
UNII — 562PDC2I9K.

Profile

Hydrastine hydrochloride, the hydrochloride of an alkaloid obtained from *Hydrastis canadensis* (Ranunculaceae) (see Hydrastis, below), has been reputed to cause uterine contractions and arrest uterine haemorrhage but it is of doubtful value. It was also formerly used in gastrointestinal disorders. Toxic doses are reported to cause strychnine-like convulsions and relaxation of the gut.

Hydrastinine Hydrochloride

Idrastinina Cloruro; Гидрастинина Гидрохлорид.
5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-ol hydrochloride.
$C_{11}H_{11}NO_3.HCl$=225.7
CAS — 6592-85-4 (hydrastinine); 4884-68-8 (hydrastinine hydrochloride).
UNII — 58253P6A1G.

Profile

Hydrastinine is a derivative of the alkaloid hydrastine (above) and has been used similarly. It has vasoconstrictor properties and has been used as the hydrochloride as an ingredient of topical preparations for minor eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Haemanal.

Hydrastis

Curcuma canadiense; Golden Seal; Goldenseal; Hidraste; Hidrastis; Hydrast; Hydrastidis Radix; Hydrastis Rhizoma; Hydrastisjuuri; Hydrastisrot; Idraste; Kanadinių auksašaknių šakniastiebiai; Sello de oro; Vodilkový kořen; Желтокорень Канадский (*Hydrastis canadensis*); Yellow Root.
UNII — ZW3Z11D0JV (goldenseal).

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Eur.* also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Goldenseal Rhizome; Goldenseal Root BP 2014). The whole or cut, dried rhizome and root of *Hydrastis canadensis* containing not less than 2.5% of hydrastine and not less than 3.0% of berberine, calculated on the dried basis. Protect from light.

Ph. Eur. 8: (Hydrastis Canadensis for Homoeopathic Preparations). Prepared from the whole or cut, dried rhizome and root of *Hydrastis canadensis*. Protect from light.

USP 36: (Goldenseal). The dried roots and rhizomes of *Hydrastis canadensis* (Ranunculaceae), containing not less than 2.0% of hydrastine and not less than 2.5% of berberine, calculated on the dried basis. Store in airtight containers. Protect from light, moisture, and heat.

Profile

Hydrastis was formerly used to arrest excessive uterine haemorrhage. It is included in some herbal preparations for gastrointestinal disorders and peripheral vascular disorders. The pharmacological activity of hydrastis is attributed mainly to 2 of its constituent alkaloids, berberine (p. 2455.1) and hydrastine (above).

Homoeopathy

Hydrastis has been used in homoeopathic medicines under the following names: Hydrastis canadensis; Hyrdr. can.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Bilberry Plus†; Cats Claw-Echine; Echinacea Royale; Euphrasia Complex; *Canad.*: Natraway Sport 1 & 2†; Natraway Sport 3†; Para-Gard; Para-Gone; *Fr.*: Climaxol; *Spain*: Solucion Schoum; *Turk.*: Ma-Ka-Ta; *UK*: Digestive; HRI Golden Seal Digestive; Wind & Dyspepsia Relief.

Homoeopathic Preparations. *Austral.*: Childrens Runny Nose Relief; Snorestop; Stomach Calm; *Austria*: Asinis; Lymphdiaral; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Otovowen; Robinia Med Complex; *Canad.*: Eczema L87; Formula CI 207†; Formula FV 213; Homeo-Form PMT†; Homeo-Form SI†; Homeodel 21†; Hylagene; Hylands Formula S; Hylands Sinus†; Indigestion; Mucan; Nareel†; PMS; Rhinar†; Sinus Ease; Sinus; Sinus; Snore Stop; Toxex; Ubicoenzyme; *Chile*: Calendula Echinacea Comp; Ovukalen; Cz.: Lamioflur†; *Fr.*: Adenocynesine†; Aesculus Compose; Allium Cepa Compose; Chelidonium Compose; Cimicifuga Complexe No 21†; Conium Complexe No 36†; Endhometrol; Hepatodrainol; Hepatopan†; Homeogene 22†; Hydrastis Compose; L 25; L 28; Pulviplasmine†; Ricinus Compose; Scabiosa Complexe No 87; Sinuspax; Thlascose†; *Ger.*: Aletris Oligoplex†; Antimas†; Gastro-Pasc; Jsostoma S; Lymphdiaral; Lymphdiaral; Mucosa compositum; Otovowen; Rapako comp; Sinuselect N; Ulco-cyl L Ho-Len-Complex; *Hung.*: Naso-Heel S; Toxex; *Neth.*: Hepatodrainol†; Lymphdiaral; Mucosa comp H; Nectadyn H; Omnilite; Opsonat; Rinileen†; Sinufleur; Snurdim; Toxex; *Port.*: Hepatodrainol; *Rus.*: Asinis (Асинис); Cinnabsin (Цинnабсин); Mastopol (Мастопол); *Switz.*: A Vogel pour les sinus; Alceprin-N; metasinusit; Nelsons Sinusit†; Regenaplex Nr. 59b; Regenaplex Nr. 71b; Sinusin; Sinuspax†; *Ukr.*: Asinis (Асинис); Cinnabsin (Цинnабсин); *USA*: Preferred Remedies Sinus.

Hydrazine Sulfate

Hidrazina, sulfato de; Hidrazine Sulfate; Hydrazine Sulphate; Hydrazyny siarczan.
$H_6N_2O_4S$=130.1
CAS — 302-01-2 (hydrazine); 10034-93-2 (hydrazine sulfate).
UNII — 1N369SAT01.

Profile

Hydrazine sulfate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinic chloride for corneal tattooing. It has been tried, but with little if any benefit, in the management of cancer-related anorexia and cachexia.

Adverse effects and treatment. References to adverse effects resulting from exposure to hydrazine.[1-5] Pyridoxine has been used in the management of hydrazine intoxication.[6-8]

1. Albert DM, Puliafito CA. Choroidal melanoma: possible exposure to industrial toxins. *N Engl J Med* 1977; 296: 634–5.
2. Durant PJ, Harris RA. Hydrazine and lupus. *N Engl J Med* 1980; 303: 584–5.
3. WHO. Hydrazine. *Environmental Health Criteria 68*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc68.htm (accessed 24/07/08)
4. WHO. Hydrazine health and safety guide. *IPCS Health and Safety Guide 56*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg056.htm (accessed 24/07/08)
5. Hainer ML *et al.* Fatal hepatorenal failure associated with hydrazine sulfate. *Ann Intern Med* 2000; 133: 877–80.
6. Kirklin JK *et al.* Treatment of hydrazine-induced coma with pyridoxine. *N Engl J Med* 1976; 294: 938–9.
7. Harati Y, Niakan E. Hydrazine toxicity, pyridoxine therapy, and peripheral neuropathy. *Ann Intern Med* 1986; 104: 728–9.
8. Nagappan R, Riddell T. Pyridoxine therapy in a patient with severe hydrazine sulfate toxicity. *Crit Care Med* 2000; 28: 2116–18.

Anorexia and cachexia. References[1-3] to the use of hydrazine sulfate in patients with anorexia or cachexia associated with cancer.

1. Tayek JA *et al.* Effect of hydrazine sulphate on whole-body protein breakdown measured by ^{14}C-lysine metabolism in lung cancer patients. *Lancet* 1987; ii: 241–4.
2. Loprinzi CL *et al.* Cancer-associated anorexia and cachexia: implications for drug therapy. *Drugs* 1992; 43: 499–506.
3. Kaegi E. Unconventional therapies for cancer: hydrazine sulfate. *Can Med Assoc J* 1998; 158: 1327–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Sehydrin (Сегидрин); *Ukr.*: Sehydrin (Сегидрин).

Hydrochloric Acid

Acide chlorhydrique; Acidum Hydrochloricum; Acidum Hydrochloridum; Clorhídrico, ácido; Cloruro de hidrógeno; E507; Kloorivetyhappo; Kwas solny; Kyselina chlorovodíková; Saltsyra; Salzsäure; Sósav; Suolahappo; Vandenilio chlorido rūgštis; Vetykloridihappo.
HCl=36.46
CAS — 7647-01-0.
ATC — A09AB03; B05XA13.
ATC Vet — QA09AB03; QB05XA13.
UNII — QTT17582CB.

NOTE. The impure acid of commerce is known as Spirits of Salt and as Muriatic Acid.

Pharmacopoeias. *Chin., Eur.* (see p. vii), *Int., Jpn, Swiss*, and *Viet.* include various concentrations. Also in *USNF*.

Ph. Eur. 8: (Hydrochloric Acid, Concentrated; Acidum Hydrochloridum Concentratum; Hydrochloric Acid BP 2014). It contains 35.0 to 39.0% w/w of HCl. A clear, colourless, fuming liquid. Miscible with water. Store below 30 degrees in stoppered containers of glass or other inert material.

Ph. Eur. 8: (Hydrochloric Acid, Dilute; Acidum Hydrochloridum Dilutum). It contains 9.5 to 10.5% w/w of HCl prepared by mixing hydrochloric acid 274 g with water 726 g.

USNF 31: (Hydrochloric Acid). It contains 36.5 to 38.0% w/w of HCl. A colourless, fuming liquid having a pungent odour. It ceases to fume when it is diluted with 2 volumes of water. Store in airtight containers.

USNF 31: (Diluted Hydrochloric Acid). It contains 9.5 to 10.5% w/v of HCl and may be prepared by mixing hydrochloric acid 226 mL with sufficient water to make 1000 mL. A colourless, odourless liquid. Store in airtight containers.

Uses and Administration

Hydrochloric acid has been used as an escharotic. It has been used in the diluted form for the treatment of achlorhydria and other gastrointestinal disorders. It has also been given intravenously in the management of metabolic alkalosis (p. 1775.3). An acid perfusion test using hydrochloric acid has been used in the diagnosis of oesophageal disorders. When taken orally, it should be sipped through a straw to protect the teeth.

Homoeopathy

Hydrochloric acid has been used in homoeopathic medicines under the following names: Acidum hydrochloricum; Muriaticum acidum; Muriaticum ac; Hydrochloridum acidum; Chlorhydricum acidum; Acidum muriaticum; Ac. mur.

Diagnosis and testing. References and comments on the use of an acid perfusion test in the diagnosis of oesophageal disorders,[1-5] such as gastro-oesophageal reflux disease (p. 1807.2) and oesophageal motility disorders (p. 1813.2). The test involves intra-oesophageal perfusion of 0.1M hydrochloric acid; subsequent development of pain indicates an acid-sensitive oesophagus. This test has also been used in the differential diagnosis of angina.[2]

1. Sladen GE *et al.* Oesophagoscopy, biopsy, and acid perfusion test in diagnosis of "reflux oesophagitis". *BMJ* 1975; 1: 71–6.
2. Anonymous. Angina and oesophageal disease. *Lancet* 1986; i: 191–2.
3. Hewson EG *et al.* Acid perfusion test: does it have a role in the assessment of non cardiac chest pain? *Gut* 1989; 30: 305–10.
4. de Caestecker JS, Heading RC. Acid perfusion in the assessment of non-cardiac chest pain. *Gut* 1989; 30: 1795–7.
5. Howard PJ *et al.* Acid perfusion is a good screening test for symptomatic oesophageal reflux. *Gut* 1989; 30: A1445.

Pregnancy. Heartburn during pregnancy may be due to reflux of alkaline duodenal contents. A dilute solution of hydrochloric acid (pH 2) taken after meals and at bedtime

produced improvements in heartburn in pregnant women.[1]

1. Anonymous. Heartburn in pregnancy. *Drug Ther Bull* 1990; 28: 11–12.

Adverse Effects

Hydrochloric acid is highly irritant and corrosive and ingestion has proved fatal. The corrosive effect causes chemical burns and severe pain. There may be violent vomiting, haematemesis, and circulatory collapse; acids can also produce intravascular coagulation and haemolysis. Ulceration may lead to perforation and patients can suffer strictures and pyloric stenosis. Asphyxiation may result from laryngeal oedema. Inhalation of acid fumes or aspiration of ingested acids may cause pneumonitis.

References.
1. WHO. Chlorine and hydrogen chloride. *Environmental Health Criteria 21*. Geneva: WHO, 1982. Available at: http://www.inchem.org/documents/ehc/ehc/ehc21.htm (accessed 16/06/04)
2. Munoz Munoz E, *et al.* Massive necrosis of the gastrointestinal tract after ingestion of hydrochloric acid. *Eur J Surg* 2001; 167: 195–8.

Treatment of Adverse Effects

Treatment of ingestion is mainly symptomatic. Gastric lavage and activated charcoal are not generally appropriate and emetics must *not* be used. Small amounts of water or milk may be given to dilute the acid but larger volumes may increase the risk of emesis and hence of further damage. Neutralising agents are not recommended because of the possibility of heat being produced during exothermic reactions, which may increase the injury further. Opioid analgesia may be required for pain. Endoscopy should be performed and surgical intervention may be necessary. There is little evidence to support the value of corticosteroids in preventing stricture formation.

Acid burns of the skin should be flooded immediately with water and the washing should be copious and prolonged. Any affected clothing should be removed while flooding is being carried out. For burns in the eye, the lids should be kept open and the eye flushed with a steady stream of water at room temperature or sodium chloride 0.9%. A few drops of a local anaesthetic solution will relieve lid spasm and facilitate irrigation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Mixtura Pepsini.

Multi-ingredient Preparations. *Ital.*: Gastro-Pepsin; *S.Afr.*: Sentinel Ulcer Mixture†.

Homoeopathic Preparations. *Austral.*: Vitatona Energy†; *Canad.*: Hae 2 Complex†; *Ger.*: Kinolymphat†; Lowe-Komplex Nr 6; *Switz.*: Regenaplex Nr 28a; Regenaplex Nr. 21e.

Hydrofluoric Acid

Fluohydric Acid; Fluorhídrico, ácido; Fluoric Acid; Fluoruro de hidrógeno; Kwas fluorowodorowy.
HF=20.01
CAS — 7664-39-3.
UNII — RGL5YE86CZ.

Description. Hydrofluoric acid is a solution of hydrogen fluoride in water. Various strengths are used. It attacks glass strongly.

Uses

Hydrofluoric acid is used in industry. Its main use has been for the production of fluorocarbons for use as refrigerants and propellants. It has also been used as an ingredient of preparations for glass etching and rust removal.

Homoeopathy

Hydrofluoric acid has been used in homoeopathic medicines under the following names: Fluoricum acidum; Acidum hydrofluoricum; Ac. fluor.; Hydrofluoricum acidum; Hydrofluoricum ac.

Adverse Effects

As for Hydrochloric Acid, above. Although the corrosive effects of hydrofluoric acid tend to predominate, absorption may produce systemic fluoride poisoning as described under Sodium Fluoride, p. 2090.1.

The pain from contact with weak solutions may be delayed, so that the patient is not aware of being burnt until some hours later, when the area begins to smart; intense pain then sets in and this may persist for several days. Destruction of tissue proceeds under the toughened coagulated skin, so that the ulcers extend deeply, heal slowly, and leave a scar.

The fumes of hydrofluoric acid are highly irritant.

Treatment of Adverse Effects

The initial treatment of poisoning after oral exposure to hydrofluoric acid is similar to that described for hydrochloric acid, see above. Calcium gluconate should also be given intravenously to correct known or suspected hypocalcaemia. Calcium chloride has also been given. Nebulised calcium gluconate may also be considered for severe poisoning by inhalation.

For ocular burns, the eye should be irrigated thoroughly for at least 30 minutes with Hexafluorine (*Prevor, Fr.*), a product containing amphoteric and chelating salts; if Hexafluorine is not available copious amounts of water or sodium chloride 0.9% should be used. Calcium gluconate has been used but there is little evidence of efficacy, and it may damage the conjunctiva.

In the event of skin burns with hydrofluoric acid, contaminated clothing or articles should be removed and the skin washed with copious amounts of cold water; Hexafluorine may be used if available. A calcium gluconate gel is sometimes used and it may be necessary to infiltrate the affected areas with calcium gluconate intradermally or subcutaneously. Regional intravenous infusion of calcium gluconate may be necessary in severe burns of the forearm, hand, or fingers; if ineffective, intra-arterial infusion for burns of the fingers may be considered. Hydrofluoric acid passes through finger- and toe-nails without causing any apparent damage; nails will therefore have to be removed or perforated to be able to treat the underlying tissues. Other first-aid measures reported to be effective include prolonged soaks in iced solutions of benzalkonium chloride; iced water has sometimes been used as has iced magnesium sulfate solution. Local anaesthesia may be needed. Burn eschars should be excised and necrotic tissue debrided. Absorption may lead to systemic fluoride toxicity and the need for intravenous calcium gluconate to manage hypocalcaemic symptoms.

References to the treatment of hydrofluoric acid burns.

1. Browne TD. The treatment of hydrofluoric acid burns. *J Soc Occup Med* 1974; 24: 80–9.
2. MacKinnon MA. Hydrofluoric acid burns. *Dermatol Clin* 1988; 6: 67–74.
3. McIvor MB. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; 5: 79–85.
4. Kirkpatrick JJR, *et al.* Hydrofluoric acid burns: a review. *Burns* 1995; 21: 483–93.
5. Sanz-Gallen P, *et al.* Hypocalcaemia and hypomagnesaemia due to hydrofluoric acid. *Occup Med (Lond)* 2001; 51: 294–5.
6. Martin HCO, Muller MJ. Hydrofluoric acid burns from a household rust remover. *Med J Aust* 2002; 176: 296.
7. Foster KN, *et al.* Hydrofluoric acid burn resulting from ignition of gas from a compressed air duster. *J Burn Care Rehabil* 2003; 24: 234–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Gel-Kam Dentinbloc; Perfect Solutions 1-Minute†; Perfect Solutions In Office Rinse†.

Homoeopathic Preparations. *Austria*: Crimax; Erbiode Haarvital; *Chile*: Bioactiv P; *Fr.*: Hamamelis Compose; Veino-Drainol†; *Switz.*: Regenaplex Nr. 21e; Regenaplex Nr. 31b.

Hydroquinine Hydrobromide

Dihydrochinin Hydrobromide; Dihydroquinine Hydrobromide; Hidroquinina, hidrobromuro de; Hydrochinin Hydrobromide; Methylhydrocupreine Hydrobromide; Гидрохинина Гидробромид.
8α,9R-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrobromide.
$C_{20}H_{26}N_2O_2,HBr$=407.4
CAS — 522-66-7 (hydroquinine).
ATC — M09AA01.
ATC Vet — QM09AA01.
UNII — Q26K81T6MC.

NOTE. Do not confuse with Hydroquinone (p. 1705.1).

Profile

Hydroquinine is a derivative of quinine (p. 665.1) used similarly in the treatment of nocturnal muscle cramps. It is given as the hydrobromide in an oral dose of 200 mg with the evening meal and a further 100 mg at bedtime for 14 days.

Muscle spasm. Quinine and its derivatives such as hydroquinine have traditionally been used for the prevention of nocturnal cramps (p. 2014.1) but there has been concern over their efficacy and potential for adverse effects, especially in the elderly.

References.
1. Jansen PHP, *et al.* Randomised controlled trial of hydroquinine in muscle cramps. *Lancet* 1997; 349: 528–32.
2. van Kan HJM, *et al.* Hydroquinine pharmacokinetics after oral administration in adult patients with muscle cramps. *Eur J Clin Pharmacol* 2000; 56: 263–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Inhibin.

Hydroxyamfetamine Hydrobromide

(BANM, rINNM) ⊗

Bromhidrato de Hidroxianfetamina; Hidrobromuro de hidroxianfetamina; Hidroxianfetamina, hidrobromuro de; Hydroxyamfetamine, Bromhydrate d-; Hydroxyamfetamini Hydrobromidum; Hydroxyamphetamine Hydrobromide; p-Hydroxyamphetamine Hydrobromide; Oxamphetamine Hydrobromide; Parahydroxyamphetamine Hydrobromide; Гидроксиамфетамина Гидробромид.
(±)-4-(2-Aminopropyl)phenol hydrobromide.
$C_9H_{13}NO,HBr$=232.1.
CAS — 103-86-6 (hydroxyamfetamine); 1518-86-1 ((±)-hydroxyamfetamine); 306-21-8 (hydroxyamfetamine hydrobromide); 140-36-3 ((±)-hydroxyamfetamine hydrobromide).
UNII — 59IG475Z0E.

Pharmacopoeias. In *US*.

USP 36: (Hydroxyamphetamine Hydrobromide). A white, crystalline powder. Freely soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Its solutions in water are slightly acid to litmus, having a pH of about 5. Protect from light.

Profile

Hydroxyamfetamine hydrobromide is a sympathomimetic with an action similar to that of ephedrine (p. 1663.2), but it has little or no stimulant effect on the CNS. It was formerly used as a vasopressor and in the management of some cardiac disorders.

In ophthalmology, hydroxyamfetamine hydrobromide has been used in a 1% solution as a mydriatic and in the diagnosis of Horner's syndrome.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Paremyd.

Pharmacopoeial Preparations

USP 36: Hydroxyamphetamine Hydrobromide Ophthalmic Solution.

Hydroxyapatite *(BAN)*

542 (edible bone phosphate); Durapatite (USAN); Hidroxiapatite; Hidroxiapatito; Hidroxilapatito; Hydroxylapatite; Win-40350; Гидроксиапатит.
Decacalcium dihydroxide hexakis(orthophosphate).
$3Ca_3(PO_4)_2,Ca(OH)_2$=1004.6; $Ca_5(OH)(PO_4)_3$=502.3
CAS — 1306-06-5.
UNII — 91D9GV0Z28.

Profile

Hydroxyapatite is a natural mineral with composition similar to that of the mineral in bone. Hydroxyapatite for therapeutic purposes is prepared from bovine bone and contains, in addition to calcium and phosphate, trace elements, fluoride and other ions, proteins, and glycosaminoglycans. It is given orally to patients requiring both calcium and phosphorus supplementation. Hydroxyapatite with tricalcium phosphate has been used in bone grafts.

Hydroxyapatite derived from marine coral has been used in the construction of orbital implants for use after surgical removal of the eye. A form of hydroxyapatite referred to as calcium hydroxyapatite (calcium hydroxylapatite; CaHA) is used for the correction of facial lipoatrophy in patients with HIV infection and as a cosmetic filler for moderate to severe facial wrinkles and folds.

Adverse effects. Reference to problems associated with the use of coral-derived orbital implants[1] and synthetic calcium hydroxyapatite.[2]

1. Shields CL, *et al.* Problems with the hydroxyapatite orbital implant: experience with 250 consecutive cases. *Br J Ophthalmol* 1994; 78: 702–6.
2. Sankar V, McGuff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J Am Dent Assoc* 2007; 138: 1093–96.

Uses. A mixture of calcium phosphates with calcium carbonate could be combined to form a paste that could be injected into acute fractures;[1] under physiological conditions the paste hardened within minutes, due to the formation of dahllite, a carbonated apatite, and held the bones in place as it was progressively replaced by living bone.

1. Constantz BR, *et al.* Skeletal repair by in situ formation of the mineral phase of bone. *Science* 1995; 267: 1796–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Ossopan; ***Braz.***: Ossopan; ***Cz.***: Osteogenon; ***Fr.***: Ossopan; ***Ger.***: Calcibon; Endobon; ***Hung.***: Osteogenon; ***India***: Calex; Calstron; Natcal; Orgacal; Ossopan; ***Indon.***: Ossopan; Ossoral; ***Irl.***: Ossopan†; ***Ital.***: Apagen; ***Mex.***: Ossopan; ***Pol.***: Ossopan; Osteogenon; ***Port.***: Ossopan†; ***Rus.***: Osteogenon (Остеогенон); ***Spain***: Osteopor; ***Switz.***: Ossopan; ***Thai.***: Ossopan; ***UK***: Osteo Support; ***Ukr.***: Osteogenon (Остеогенон); ***USA***: Radiesse.

Multi-ingredient Preparations. ***Arg.***: Totalos Plus; ***Austral.***: Bone Builder; PM NextG Cal; ***Canad.***: Osteo-Guard†; ***Ger.***: Collapat II; ***India***: Odical; ***Indon.***: Vossecal; ***Ital.***: Eugune.

Hydroxymethylnicotinamide

Hidroximetilnicotinamida; *N*-Hydroxymethylnicotinamide; Nicotinylmethylamide; Nicotinylmethylamidum; Nikotynylometyloamid; Гидроксиметилникотинамид.

N-Hydroxymethylpyridine-3-carboxamide.

$C_7H_8N_2O_2$=152.2

CAS — 3569-99-1.

ATC — A05AB01.

ATC Vet — QA05AB01.

Pharmacopoeias. In *Pol.*

Profile

Hydroxymethylnicotinamide is a cholagogue and has been used in the treatment of various disorders of the gallbladder.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Bilamide†.

Multi-ingredient Preparations. ***India***: Jetositol.

Hydroxyquinoline Sulfate

Chinosolum; Hidroxiquinolina, sulfato de; Hydroxyquinoline Sulphate; Oksikinoliinisulfaatti; Oxichinolini Sulfas; Oxikinolinsulfat; Oxine Sulphate; Oxiquinol; Oxyquinol; Oxyquinoline Sulfate (USAN); Sulfate d'Orthoxyquinoléine; Гидроксихинолина Сульфат.

Quinolin-8-ol sulphate; 8-Quinolinol sulphate.

$(C_9H_7NO)_2,H_2SO_4$=388.4

CAS — 148-24-3 (hydroxyquinoline); 134-31-6 (hydroxyquinoline sulfate).

ATC — A01AB07; D08AH03; G01AC30; R02AA14.

ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

UNII — 61VUG75Y3P.

Pharmacopoeias. In *Fr.* and *Swiss.* Also in *USNF.*

USNF 31: (Oxyquinoline Sulfate). A yellow powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether; freely soluble in methyl alcohol.

Potassium Hydroxyquinoline Sulfate

Oxiquinol potásico; Oxyquinol Potassium; Potassii Hydroxyquinolini Sulphas; Potassium Hydroxyquinoline Sulphate; Potassium Oxyquinoline Sulphate; Sulfato de hidroxiquinolina potásica.

CAS — 14534-95-3.

ATC — A01AB07; D08AH03; G01AC30; R02AA14.

ATC Vet — QA01AB07; QD08AH03; QG01AC30; QR02AA14.

Pharmacopoeias. In *Br.*, *Fr.*, and *Ger.*

BP 2014: (Potassium Hydroxyquinoline Sulfate). An equimolecular mixture of potassium sulfate and quinolin-8-ol sulfate monohydrate. It contains 50.6 to 52.6% of quinolin-8-ol and 29.5 to 32.5% of potassium sulfate, calculated with reference to the anhydrous substance. A pale yellow, odourless or almost odourless, microcrystalline powder. Freely soluble in water; insoluble in ether. On extraction with hot dehydrated alcohol a residue of potassium sulfate and a solution of quinolin-8-ol sulfate are obtained.

Profile

Hydroxyquinoline sulfate and potassium hydroxyquinoline sulfate have antibacterial, antifungal, and deodorant properties, and have been used similarly in the topical treatment of skin, oropharyngeal, and vaginal disorders. Potassium hydroxyquinoline sulfate is often used with benzoyl peroxide.

Derivatives of hydroxyquinoline including the salicylate, benzoate, borate, hydrofluoride, iodochloride, silicofluoride, and sodium hydroxyquinoline sulfate have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Leioderm†; ***Ital.***: Aftir Shampoo; ***Neth.***: Superol†.

Multi-ingredient Preparations. ***Arg.***: Curisept; ***Braz.***: Andolba; Cerumin; Colpolase†; Lacto Vagin; Malvatricin Ginecologico†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatricin; ***Canad.***: Racestyptine; ***Chile***: Diproquin; ***Fr.***: Chromargon; Dermacide; Nestosyl†; Nestosyl; ***Ger.***: Chinosol; Leioderm P; ***Gr.***: Dermacide; ***Irl.***: Quinoderm; ***Ital.***: Disinfene†; Ustiosan; ***Port.***: Queimax; ***Rus.***: Combutec-2 (Комбутек-2); Contraceptin T (Контрацептин Т); ***S.Afr.***: Oto-Phen Forte†; Quinoderm†; Universal Earache Drops†; ***Switz.***: Benzocaine FD; Rectoseptal-Neo bismuthe; Rectoseptal-Neo simple; ***UK***: Quinoderm; Valderma; ***USA***: Acid Jelly†; Aurax; Auroguard Otic; Fem pH; Oxyzal; Stypto-Caine; Trimo-San; Triv; ***Venez.***: Borogin.

Pharmacopoeial Preparations

BP 2014: Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream.

Hymecromone *(BAN, USAN, rINN)*

Himecromona; Himekromon; Himekromonas; Hymechromon; Hymecromon; Hymécromone; Hymecromonum; Hymekromon; Hymekromoni; Imecromone; LM-94; Гимекромон.

7-Hydroxy-4-methylcoumarin.

$C_{10}H_8O_3$=176.2

CAS — 90-33-5.

ATC — A05AX02.

ATC Vet — QA05AX02.

UNII — 3T5NG4Q468.

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

Ph. Eur. 8: (Hymecromone). An almost white crystalline powder. Very slightly soluble in water; slightly soluble in dichloromethane; sparingly soluble in methyl alcohol. It dissolves in dilute solutions of ammonia. Protect from light.

Profile

Hymecromone is a choleretic and biliary antispasmodic. It has been given orally in doses of 400 mg three times daily at mealtimes. It has also been given as the sodium salt by slow intravenous injection as an adjunct to diagnostic procedures. Diarrhoea may occasionally occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Unichol†; ***Belg.***: Cantabiline; ***Cz.***: Cholestil; Isochol; ***Fr.***: Cantabiline; ***Ger.***: Chol-Spasmoletten; Cholspasmin; ***Gr.***: Cantabiline; Choliren; ***Ital.***: Cantabilin; ***Pol.***: Cholestil; ***Rus.***: Odeston (Одестон); ***Turk.***: Cantabilin.

Hyoscyamus

Banotu; Beleño; Bilsenkraut; Bolmört; Giusquiamo; Henbane; Hullukaali; Hyoscy.; Hyoscyami; Hyoscyami folium (hyoscyamus leaf); Jusquiame; Jusquiame Noire; Jusquiame noire, feuille de (hyoscyamus leaf); Meimendro; Белена.

ATC Herb — HR03BB5002 (Hyoscyamus niger: seed); HA03YA5004 (Hyoscyamus niger: herb); HA03YA5006 (Hyoscyamus niger: seed); HA03YA5005 (Hyoscyamus niger: leaf).

UNII — 34412PDT5E (Hyoscyamus niger); 4WRK2F53H3 (Hyoscyamus niger flowering); 32IT7G8BAW (Hyoscyamus niger leaf).

Pharmacopoeias. *Chin.* specifies only the seeds.

Eur. (see p. vii) includes a form for homoeopathic preparations.

Ph. Eur. 8: (Hyoscyamus for Homoeopathic Preparations; Hyoscyamus Niger ad Praeparationes Homoeopathicas). The whole, fresh flowering plant of *Hyoscyamus niger*. Protect from light.

Profile

Hyoscyamus contains the alkaloid hyoscyamine with varying amounts of hyoscine and has peripheral and central effects similar to those of atropine (p. 1312.1); its preparations have been used mainly for the relief of visceral spasm. The fresh whole flowering plant (*Hyoscyamus niger*) as well as the dried leaves have been used in herbal and medicine.

Homoeopathy

Hyoscyamus has been used in homoeopathic medicines under the following names: Hyoscyamus leaf; Hyoscyamus niger; Hyos. nig.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Kelosoft; ***Switz.***: Kelosoft; ***Venez.***: Atroveran.

Multi-ingredient Preparations. ***Arg.***: Hepacur; ***Austria***: Cardiodoron; ***Braz.***: Ductoveran; Glicodin; MM Expectorante; ***Chin.***: Kang Ming (康明); ***Fr.***: Laccoderme a l'huile de cade†; ***Ger.***: Cardiodoron; Cimicifuga comp; Unguentum lymphaticum; ***India***: Elixir Efelin; Memtone; Neo-Cordial; ***Port.***: Doce Alivio; ***S.Afr.***: Cardiodoron†; ***Switz.***: Cardiodoron; Keli-med; Sirop pectoral contre la toux S; ***UK***: Onopordon Comp B; ***Venez.***: Atrobel; Linfoderm.

Homoeopathic Preparations. ***Austral.***: Respatona Dry Cough & Nasal Congestion; Sleep & Insomnia Relief; ***Austria***: Bronchalis-Heel; ***Canad.***: Bronkeel†; Formula C Doron†; Formula D Doron†; Homeo-Form I†; Homeo-Form PMT†; Homeogene 46; Hylands Insomnia; Insomnia; Kids Calm; PMS; Quietude; Spa Complex†; Stress L72†; ***Cz.***: Bronchalis-Heel; Sedalia; ***Fr.***: Abbe Chaupitre no 7; Boripharm No 3; Dolirelax†; Homeogene 46; Ipeca Complexe No 65; L 72; Lobelia Complexe No 74; Oenanthe Crocata Complexe No 78; Quietude; Tarentula Complexe No 71; Zincum Cyanidum Complexe No 101†; ***Ger.***: Ambrax; Aralis; Bomapect N; Bronchi-Do; Broncho-Entoxin N; Cordiodoron†; Crataegus comp; Monapax; Passiflora Complex†; Roth's RKT Tropfen; Tussiflorin Hom; Zincum Hevert N; ***Hung.***: Bronchalis-Heel; ***Neth.***: Bronchalis; Quietude†; ***Rus.***: Valeriana Plus (Валериана-Плюс); ***Switz.***: Bronchalis-Heel; Quietude; ***Ukr.***: Homvio-Nervin (Хомвио-Нервин).

Hypoglycin A

Hipoglicina A.

L-2-Amino-3-(2-methylenecyclopropyl)propionic acid.

$C_7H_{11}NO_2$=141.2

CAS — 156-56-9.

Profile

Hypoglycin A is a toxic substance present in the arillus of unripe ackee (akee), the fruit of *Blighia sapida* (Sapindaceae). It is responsible for Jamaican vomiting sickness, with symptoms of acute and severe vomiting, hypoglycaemia, muscular weakness, CNS depression, convulsions, and coma, frequently fatal. Glycine has been suggested for the management of hypoglycin A toxicity.

Hypophosphorous Acid

Ácido fosfínico; Acidum Hypophosphorosum; Hipofosforoso, ácido; Phosphinic Acid; Гипофосфористая Кислота; Фосфорноватистая Кислота.

H_3PO_2=66.0

CAS — 6303-21-5; 14332-09-3.

Pharmacopoeias. In *USNF.*

USNF 31: (Hypophosphorous Acid). It contains 30 to 32% of H_3PO_2. A colourless or slightly yellow, odourless liquid. Store in airtight containers.

Profile

Hypophosphorous acid is used as an antioxidant. Salts of hypophosphorous acid (hypophosphites or phosphinates) have been used in tonics, although they are not considered a suitable source of phosphorus.

Homoeopathy

Calcium hypophosphite has been used in homoeopathic medicines under the following names: Calcarea hypophosphorosa; Calc. hyp.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Pectobron; ***Braz.***: Rhum Creosotado†; ***Canad.***: Toniminet†; ***Gr.***: Calvicef; ***Hong Kong***: Scott's Emulsion Orange†; Scott's Emulsion Original†; ***Hung.***: China; ***India***: Kalzana; ***Indon.***: Bionutrion; Curvit CL; Scott's Emulsion Vita; Scott's Emulsion Vita; Scott's Emulsion; Vical; Vidoran Emulsion Rasa; ***UK***: Dispello; S.P.H.P..

Homoeopathic Preparations. ***Fr.***: Jenoverine†; L 25; ***Ger.***: Ekzem-Entoxin N; Psychoneuroticum (Rowo-578)†; ***Neth.***: Jenoverine†; ***Ukr.***: Kindinorm (Киндинорм).

Hyssop

Herba Hyssopi; Hysope; Hyssop Wort; Ysop; Иссоп.

ATC Herb — HR05YA5010 (Hyssopus officinalis: herb); HR05YA5009 (Hyssopus officinalis: essential oil).

UNII — X7HKN4FOJF (hyssop); 173D71924B (hyssop oil); 0IQW00TKPE (Hyssopus officinalis).

Pharmacopoeias. In *Fr.*

Profile

Hyssop is the fresh or dried aerial parts of *Hyssopus officinalis* (Lamiaceae). The herb and its preparations are included in herbal preparations mainly for disorders of the gastrointestinal and upper respiratory tracts.

It is the source of hyssop oil which is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Adelgazar; Arceligasol; *Austria*: The Chambard-Tee; *Canad.*: Clear Capsules†; Swiss Herb Cough Drops; *Hung.*: Gombarex; *Ital.*: Tisana Kelemata; *Pol.*: Pectosol; *Rus.*: Linkus (Линкас); Linkus Lor (Линкас Лор); *Spain*: Agua del Carmen; *UK*: Catarrh Mixture; Covonia Catarrh Relief; Tickly Cough & Sore Throat Relief; Vegetable Cough Remover; *Ukr.*: Linkus (Линкас); Pectolvan Phyto (Пектолван Фито).

Ibogaine

Ibogaina; NIH-10567.
12-Methoxyibogamine.
$C_{20}H_{26}N_2O$=310.44.
CAS — 83-74-9.
UNII — 3S814I130U.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of ibogaine or preparations containing ibogaine:

Iboga.

Profile

Ibogaine is a hallucinogenic indole alkaloid extracted from the West African shrub *Tabernanthe iboga* (Apocynaceae). It has been investigated as an aid to withdrawal from drug addiction.

References.

1. Popik P, *et al.* 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol Rev* 1995; **47**: 235–53.
2. Alper KR, *et al.* Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999; **8**: 234–42.
3. Pace CJ, *et al.* Novel iboga alkaloid congeners block nicotinic receptors and reduce drug self-administration. *Eur J Pharmacol* 2004; **492**: 159–67.
4. Hittner JB, *et al.* Combating substance abuse with ibogaine: pre- and posttreatment recommendations and an example of successive model fitting analyses. *J Psychoactive Drugs* 2004; **36**: 191–9.
5. Maciulaitis R, *et al.* Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. *Hum Exp Toxicol* 2008; **27**: 181–94.
6. Hoelen DWM, *et al.* Long-QT syndrome induced by the antiaddiction drug ibogaine. *N Engl J Med* 2009; **360**: 308–9.

Icatibant Acetate *(BANM, USAN, rINNM)*

Acetato de icatibanto; Hoe-140 (icatibant or icatibant acetate); Icatibant, Acétate d'; Icatibanti Acetas; JE-049 (icatibant); Икатибанта Ацетат.

(*R*)-Arginyl-(*S*)-arginyl-(*S*)-prolyl-(2*S*,4*R*)-(4-hydroxyprolyl)glycyl-(*S*)-[3-(2-thienyl)alanyl]-(*S*)-seryl-(*R*)-[(1,2,3,4-tetrahydro-3-isoquinolyl)-carbonyl]-(2*S*,3a*S*,7a*S*)-[(hexahydro-2-indolinyl)-carbonyl]-(*S*)-arginine acetate.

$C_{59}H_{89}N_{19}O_{13}S.xC_2H_4O_2$

CAS — 130308-48-4 (icatibant); 138614-30-9 (icatibant acetate).
ATC — B06AC02.
ATC Vet — QB06AC02.
UNII — 325O8467XK.

Profile

Icatibant acetate is a selective bradykinin B_2 antagonist used in the symptomatic treatment of acute attacks of hereditary angioedema (p. 2485.2) in adults with complement C1 esterase inhibitor deficiency.

Icatibant acetate is given by subcutaneous injection, preferably into the abdomen, in a dose equivalent to 30 mg of icatibant. Due to the large injection volume of 3 mL, it should be given slowly. A single dose is usually enough to treat an acute attack but a second dose may be given after 6 hours if required. Not more than 3 doses should be given in a 24-hour period, each given at 6-hourly intervals.

Mild and transient injection-site reactions, including erythema, swelling, warm sensation, burning, itching, and skin pain are common. Nausea, vomiting, headache, dizziness, asthenia, nasal congestion, and rashes have also been reported.

Icatibant should be given with caution to patients with acute ischaemic heart disease or unstable angina pectoris, and to patients who have recently had a stroke.

Reviews.

1. Cruden NL, Newby DE. Therapeutic potential of icatibant (HOE-140, JE-049). *Expert Opin Pharmacother* 2008; **9**: 2383–90.
2. Dubois EA, Cohen AF. Icatibant. *Br J Clin Pharmacol* 2010; **69**: 425–6.
3. Cicardi M, *et al.* Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010; **363**: 532–41. Correction. *ibid.*; 1486.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Firazyr; *Austria*: Firazyr; *Cz.*: Firazyr; *Denm.*: Firazyr; *Fr.*: Firazyr; *Ger.*: Firazyr; *Gr.*: Firazyr; *Irl.*: Firazyr; *Israel*: Firazyr; *Neth.*: Firazyr; *Norw.*: Firazyr; *Pol.*: Firazyr; *Port.*: Firazyr; *Rus.*: Firazyr (Фиразир); *Spain*: Firazyr; *Swed.*: Firazyr; *Switz.*: Firazyr; *UK*: Firazyr; *USA*: Firazyr.

Iceland Moss

Islandiniu kerpenų gniužulas; Isländisches Moos; Isländisches Moos/Isländische Flechte; Islandslav; Islanninjäkälä; Izlandi zuzmó; Lichen d'Islande; Lichen Islandicus; Lišejnik islandski; Porost islandzki; Исландский Мох.

ATC — Herb — HA01WB5002 (Cetraria islandica: thallus); HR05WA5003 (Cetraria islandica: thallus); HA09WA5005 (Cetraria islandica: thallus).
UNII — 8J7YPN79A1.

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

Ph. Eur. 8: (Iceland Moss; Lichen Islandicus). The whole or cut dried thallus of *Cetraria islandica*. Protect from light.

Profile

Iceland moss, *Cetraria islandica* (Parmeliaceae), is a lichen with demulcent and mild antimicrobial activity. It is included in herbal medicines for dry cough, and irritation or inflammation of the oral and pharyngeal mucosa. It is also used as a bitter to stimulate the appetite.

Iceland moss has been used as a foodstuff and a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Tetesept Hals-activ; *Ukr.*: Isla-Mint (Исла-Минт); Isla-Moos (Исла-Моос).

Multi-ingredient Preparations. *Ger.*: Cefabronchin; *Ital.*: Enatus; Kevis; Sclerovis H Plus; *Pol.*: Padma 28; Pectosol; *Port.*: Bioclin Sebo Care; *Switz.*: Arteria-vita; Kernosan Elixir; Padma 28; Padmed Circosan; Tisane pectorale et antitussive; *UK*: Herb and Honey Cough Elixir; Padma 28; Padma Circosan; *Ukr.*: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. *Canad.*: Kids Cough & Cold Phytux; Phytotux H; *Fr.*: Cetraria Complexe No 61; *Ger.*: A-Bomin; Cerivikehl; Drosera-Weliplex†; HanoTussan.

Idanpramine

Idampramina; Иданпрамин.

5,5-Bis(4-methoxyphenyl)-3-[2-(1-piperidinyl)ethyl]-2,4-imidazolidinedione.

$C_{24}H_{29}N_3O_4$=423.5.
CAS — 25466-44-8.
ATC — A03AX06.
ATC Vet — QA03AX06.
UNII — 8WO2013UA.

Idanpramine Hydrochloride

Иданпрамина Гидрохлорид.

$C_{24}H_{29}N_3O_4.HCl$=460.0
CAS — 25466-21-1.
ATC — A03AX06.
ATC Vet — QA03AX06.
UNII — 481367ZCIP.

Idanpramine Sulfate

Idampramina Sulfato; Иданпрамина Сульфат.

ATC — A03AX06.
ATC Vet — QA03AX06.

Profile

Idanpramine is an antimuscarinic that has been used as the hydrochloride and sulfate salts in the relief of visceral spasms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Gastroidam†.

Idursulfase *(BAN, USAN, rINN)*

Iduronate-2-sulfatase; Idursulfasa; Idursulfasum; Idusulfase; Идурсульфаз.

α-L-Iduronate sulfate sulfatase.

CAS — 50936-59-9.
ATC — A16AB09.
ATC Vet — QA16AB09.
UNII — 5WBJGG2651.

Uses and Administration

Idursulfase is recombinant human iduronate-2-sulfatase used as enzyme replacement therapy in the treatment of mucopolysaccharidosis II (see below). It is given by intravenous infusion in a dose of 500 micrograms/kg once a week. Idursulfase should be diluted in 100 mL of sodium chloride 0.9% and infused over 1 to 3 hours. The initial infusion rate should be 8 mL/hour for the first 15 minutes, which may then be increased by 8 mL/hour every 15 minutes if well tolerated, up to a maximum rate of 100 mL/hour. If the infusion rate is decreased because of infusion reactions (see below), the infusion time should not exceed 8 hours.

Administration in children. Children aged 16 months or older may be given idursulfase in the treatment of mucopolysaccharidosis II; the dosage is as described for adults, see Uses and Administration, above. Clinical experience with idursulfase treatment in children less than 5 years of age is limited; however, decreases in liver and spleen volumes and a reduction in the urine output of glycosaminoglycans similar to that seen in older children and adults have been reported.[1,2]

1. Muenzer J, *et al.* Idursulfase treatment of Hunter syndrome in children younger than 6 years: results from the Hunter Outcome Survey. *Genet Med* 2011; **13**: 102–9.
2. Giugliani R, *et al.* A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4–7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. *Genet Med* 2013;. Available at: doi: 10.1038/gim.2013.162

Mucopolysaccharidosis II. Mucopolysaccharidosis II (Hunter syndrome) is a rare X-linked progressive disorder occurring almost exclusively in males and characterised by inherited deficiency of the enzyme iduronate-2-sulfatase, which is necessary to catalyse a step in the breakdown of glycosaminoglycans. This results in accumulation of dermatan and heparan sulfate in lysosomes and produces widespread irreversible cellular and tissue damage and organ dysfunction. Clinical manifestations include severe respiratory obstruction, facial dysmorphism, skeletal and joint deformities, cardiomyopathy, and neurological decline, with death usually in the second decade of life, although patients with milder disease may survive well into adulthood.[1-3]

Significant morbidity and functional problems occur and treatment is supportive and symptomatic involving many body systems; physical and occupational therapy is also necessary. Idursulfase is recombinant human iduronate-2-sulfatase used as enzyme replacement therapy and has been reported to confer benefit with an acceptable safety profile. It is anticipated that greatest benefit would be seen when treatment is started as early in the course of the disease as possible, especially before serious neurological involvement has occurred since idursulfase does not cross the blood-brain barrier. Haematopoietic stem-cell transplantation to supply the deficient enzyme has been tried in some patients, although results have been disappointing and the procedure is associated with significant morbidity and mortality.[1-3]

1. Wraith JE, *et al.* Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. *Eur J Pediatr* 2008; **167**: 267–77.
2. Martin R, *et al.* Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics* 2008; **121**: e377–e386. Available at: http://pediatrics.aappublications.org/cgi/content/full/121/2/e377 (accessed 23/02/10)
3. Muenzer J, *et al.* Multidisciplinary management of Hunter syndrome. *Pediatrics* 2009; **124**: e1228–e1239. Available at: http://pediatrics.aappublications.org/cgi/content/full/124/6/e1228 (accessed 23/02/10)

Adverse Effects, Treatment, and Precautions

Infusion reactions are common with idursulfase and have included rash, pruritus, urticaria, flushing, fever, headache, and hypertension. Treatment with antipyretics, antihistamines with or without corticosteroids, or a reduction in infusion rate may be necessary. Stopping the infusion should be considered in severe reactions. Anaphylactoid reactions have been reported, in some cases up to 24 hours after the infusion. Serious adverse effects that have also been reported with idursulfase include hypoxia, pulmonary embolism, cyanosis, respiratory failure, cardiac arrhythmias, and arthralgia.

IgG antibodies to idursulfase develop in about half of patients. The presence of antibodies may predispose patients to developing infusion or allergic reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Elaprase; ***Belg.***: Elaprase; ***Canad.***: Elaprase; ***Cz.***: Elaprase; ***Denm.***: Elaprase; ***Fr.***: Elaprase; ***Ger.***: Elaprase; ***Gr.***: Elaprase; ***Hong Kong***: Elaprase; ***Hung.***: Elaprase; ***Irl.***: Elaprase; ***Israel***: Elaprase; ***Jpn***: Elaprase; ***Malaysia***: Elaprase; ***Neth.***: Elaprase; ***Norw.***: Elaprase; ***NZ***: Elaprase; ***Pol.***: Elaprase; ***Port.***: Elaprase; ***Spain***: Elaprase; ***Swed.***: Elaprase; ***Switz.***: Elaprase; ***UK***: Elaprase; ***USA***: Elaprase.

Ignatia

Fève de Saint-Ignace; Ignatia amara; Ignatius Bean; Lu Song Guo; St Ignatius' Bean.

ATC Herb — HA09WA5023 (Strychnos ignatii: seed).

UNII — 1NM3M2487K.

Profile

Ignatia consists of the dried ripe seeds of *Strychnos ignatii* (*S. tieute*; *I. amara*) (Loganiaceae). Ignatia contains strychnine (p. 2623.2) in higher concentrations than those found in Nux Vomica (p. 2573.3), plus similar concentrations of brucine, and has been used in herbal tonic preparations and as a bitter.

Homoeopathy

Ignatia has been used in homoeopathic medicines under the following names: Iamara; Ignatia amara; Ign.; Strychnos ignatii.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Nervatona Calm; Nervatona Focus.

Homoeopathic Preparations. ***Austral.***: Childrens Sleep; Nervatona Calm; Nervatona Focus; Smoke Eze; ***Austria***: Berberis Cosmoplex†; Ignatia-Homaccord; Klimaktoplant; Mandragora Med Complex; Mastodynon; Nervoheel; Pascofemin; Pasconal; Relax; Vomitusheel; ***Canad.***: Fibromyalgie; Hylands Gas; Hylands Insomnia; Kids Calm; Nixotinex; Sedilor†; Stress L72†; Stress; ***Chile***: Bioactiv O; ***Cz.***: Hormeel S; Mastodynon; Vita C-R15 forte†; Vita C-R15†; Ypsiloheel; ***Fr.***: Abbe Chaupitre no 7; Anxietum; Boripharm No 3; Dolirelax†; Dolisedal†; Dolitravel†; L 72; Lobelia Complexe No 74†; Neurocynesine†; Passiflora Compose; Soludor; Staphysagria Complexe No 92†; Stressdoron; Tabacum Compose; Tarentula Complexe No 71; Vinicard†; Zenalia; ***Ger.***: Ambrax; Antimast TN†; Calmvalera; Cefaneuro; Corselect N; Cranio-cyl Ho-Len-Complex; Gastroplant; Goldtropfen S; Hyperforat Nervo; Klimaktoplant N; Mastodynon; Myonasan; Nervoject F; Nervoregin comp; Pascofemin; Pascolibrin; Pasconal Nerventropfen; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Rytesthin; Sedaphin†; Sedaselect; Sedativa-Injektopas; Sepia comp; Ypsiloheel N; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; ***Hung.***: Hormeel S; Klimakt-Heel; Nervoheel; PSY-Stabil; ***Neth.***: Cerebrum comp; Echilite; Emvita 11; Hyperilite; Klimaktolan; Mastodynon†; Nervival; Nervofleur; Nervoheel; Neurocynesine†; PSY-stabil; ***Rus.***: Crataegus-Plus (Кратегус-Плюс); Hormeel SN (Гормель СН); Klimaktoplan (Климактоплан); Mastodynon (Мастодинон); Uspokoi (Успокой); Valeriana-Plus (Валериана-Плюс); ***Switz.***: Ignatia-Homaccord; Menosan†; Nervoheel; Vomitusheel; ***Thai.***: Mastodynon†; ***Ukr.***: Aurocard (Аурокард); Homvio-Nervin (Хомвио-Нервин); Klimaktoplan N (Климактоплан Н); Mastodynon (Мастодинон); ***USA***: Preferred Remedies Fatigue; Preferred Remedies Sleep.

Indian Barberry

Chitra; Indian Berberry; Tree Turmeric; Барбарис Остистый (*Berberis aristata*).

Pharmacopoeias. In *Br.*

BP 2014: (Berberis Aristata). The dried cut stem of *Berberis aristata*. It contains not less than 1.4% of berberine calculated with reference to the dried material.

Protect from moisture.

Profile

The stem and root bark of the Indian barberry (*Berberis aristata* (Berberidaceae)) is used orally in herbal medicine mainly for fevers, and in hepatic and gastrointestinal disorders and topically for skin lesions. The fruit and other parts of the plant are also used.

Berberis aristata is a source of berberine (p. 2455.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Antisept†; Britesite; Diabecon; Entrostat; Femi Forte; Geriforte; Geriforte; Herbinol; Livomyn; Livomyn; Livto; Marc Free; Paedritone; ***Ital.***: Berart; ***Rus.***: Bonjigar (Бонджигар); Entoban (Энтобан); Pilex (Пайлекс); ***Ukr.***: Bonjigar (Бонджигар); Entoban (Энтобан).

Indian Gooseberry

Amalaki; Amla; Emblic; Emblic Myrobalan; Филлантус Лекарственный.

ATC Herb — HA02WX5002 (Phyllanthus emblica: fruit); HA03AW5046 (Phyllanthus emblica: fruit); HA06AX5007 (Phyllanthus emblica: fruit); HA11WA5003 (Phyllanthus emblica: fruit); HA06AX5006 (Phyllanthus emblica: flower).

NOTE. The common name myrobalan or myrobalans refers to several unrelated fruit-bearing plant species from the genera *Emblica* (*Emblica officinalis*, Emblic Myrobalan or Indian Gooseberry, above), *Prunus* (*P. cerasifera*, Myrobalan Plum), and *Terminalia* (*T. arjuna*, Arjun Myrobalan — see Arjuna, p. 2447.2; *T. bellirica* — see Beleric Myrobalan, p. 2453.2; and *T. chebula* — see Chebulic Myrobalan, p. 2474.3). Care should be taken to distinguish between them.

The name Terminalia has been applied to all the myrobalans mentioned above from the *Terminalia* genus and, again, care should be taken to avoid confusion.

Pharmacopoeias. *Br.* includes Phyllanthus Emblica Pericarp.

BP 2014: (Phyllanthus Emblica Pericarp). The pericarp of dried mature fruits of *Phyllanthus emblica* (*E. officinalis*). It contains not less than 6.0% tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

The fruits of the Indian Gooseberry, *Phyllanthus emblica* (*Emblica officinalis*, *Mirobalanus embilica*) (Euphorbiaceae), have traditionally been used in Ayurvedic medicine and are included in herbal preparations.

The traditional Ayurvedic medicine triphala is a combination of Indian gooseberry, beleric myrobalan (p. 2453.2), and chebulic myrobalan (p. 2474.3). The fruits are reputed to contain large amounts of vitamin C, and are also used as a foodstuff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Vita Jam; ***Thai.***: Compound Makham Pom.

Multi-ingredient Preparations. ***Arg.***: Recover Whitening; ***Austral.***: Ultra Calm; ***Fr.***: Triphala; ***Hung.***: Herbadict; Munipyrin; ***India***: Anti Dysp; Flexi-muv†; ***Malaysia***: Bonnisan; ***Philipp.***: Cogent db+; ***Rus.***: Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Fitovit (Фитовит); Pilex (Пайлекс); Travisil (Трависил); ***Singapore***: Hemoglo; Imunomet; Septilin; Septilin; ***Thai.***: Couffee Mixture; Iyara Ma-Weang; ***Ukr.***: Alfagin (Алфагин); Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Doktor Mom Herbal Cough Lozenges (Доктор Мом Растительные Пастилки От Кашля); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†; Intellan (Интеллан); Septilin (Септилин); Travisil (Трависил); Trypsidan (Трипсидан)†.

Indigo Carmine

Blue X; Carmin de Indigo; Ceruleinum; CI Food Blue 1; Colour Index No. 73015; Disodium Indigotin-5,5′-disulphonate; E132; FD & C Blue No. 2; Indicarminum; Indigo Carmin; Indigotina; Indigotindisulfonate Sodium; Indigotine; Indygokarmin; Sodium Indigotindisulphonate; Индигокармин.

Disodium 3,3′-dioxo-2,2′-bi-indolinylidene-5,5′-disulphonate.

$C_{16}H_8N_2Na_2O_8S_2$=466.3

CAS — 483-20-5 (indigotin-5,5′-disulphonic acid); 860-22-0 (indigo carmine).

ATC — V04CH02.

ATC Vet — QV04CH02.

UNII — X7OI7JF73P (indigotin-5,5′-disulphonic acid); D3741U8K7L (indigo carmine); L06K8R7DQK (FD & C blue no 2).

NOTE. The name Cerulein has been applied to Ceruletide (p. 2473.3).

Although the name FD & C Blue No.2 is widely used to denote indigo carmine it is actually defined as being mainly indigo carmine with smaller amounts of the disodium salt of 2-(1,3-dihydro-3-oxo-7-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid (*CAS*—54947-75-0) and the sodium salt of 2-(1,3-dihydro-3-oxo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid (*CAS*—605-18-5).

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

USP 36: (Indigotindisulfonate Sodium). A dusky, purplish-blue powder, or blue granules having a coppery lustre. Soluble 1 in 100 of water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Its solutions have a blue or bluish-purple colour. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

On intravenous injection indigo carmine is rapidly excreted, mainly by the kidneys. It has been used in a test of renal function, but has largely been replaced by agents that give more precise results. It is used as a marker dye, particularly in urological procedures, when it is given in a usual dose of 40 mg, preferably by intravenous injection but sometimes intramuscularly. It has also been used as a marker dye in amniocentesis.

Indigo carmine has been used as a blue dye in medicinal preparations but it is relatively unstable. It has also been investigated as a dye-spray in the detection of colorectal adenomas. It is used as a food colour.

Adverse Effects and Precautions

Indigo carmine may cause nausea, vomiting, hypertension, and bradycardia, and occasionally, hypersensitivity reactions such as rashes, pruritus, and bronchoconstriction. Skin discoloration may occur after large parenteral doses, particularly in children and underweight patients.

Hypersensitivity. Cardiac arrest after a dose of indigo carmine 80 mg intravenously resulted in the deaths of 2 elderly patients.[1] Both had a history of asthmatic bronchitis. A life-threatening anaphylactoid reaction associated with indigo carmine use has also been reported, although the authors commented that such events are rare.[2]

1. Voiry AM, *et al.* Deux accidents mortels lors d'une injection peropératoire de carmin d'indigo. *Ann Med Nancy* 1976; **15**: 413–19.
2. Gousse AE, *et al.* Life-threatening anaphylactoid reaction associated with indigo carmine intravenous injection. *Urology* 2000; **56**: 508.

Preparations

Pharmacopoeial Preparations

USP 36: Indigotindisulfonate Sodium Injection.

Indocyanine Green

Verde de indocianina; Индоцианин Зеленый.

Sodium 2-[7-[1,1-dimethyl-3-(4-sulphobutyl)benz[*e*]indolin-2-ylidene]hepta-1,3,5-trienyl]-1,1-dimethyl-1*H*-benz[*e*]indolio-3-(butyl-4-sulphonate).

$C_{43}H_{47}N_2NaO_6S_2$=775.0

CAS — 3599-32-4.

UNII — IX6J1063HV.

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

USP 36: (Indocyanine Green). An olive-brown, dark green, blue-green, dark blue, or black powder. Is odourless or has a slight odour. It contains not more than 5.0% of sodium iodide, calculated on the dried basis. Soluble in water and in methyl alcohol; practically insoluble in most other organic solvents. Its solutions are deep emerald-green in colour. pH of a 0.5% solution in water is about 6. Its aqueous solutions are stable for about 8 hours. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Indocyanine green is an indicator dye used for assessing cardiac output and liver function, and for examining the choroidal vasculature in ophthalmic angiography. It is also used to assess blood flow and haemodynamics in various organs including the liver.

The usual dose for cardiac assessment is 5 mg injected rapidly via a cardiac catheter. A suggested dose for children is 2.5 mg, and for infants 1.25 mg. Several doses need to be given to obtain a number of dilution curves. However, the total dose should not exceed 2 mg/kg.

The usual dose of indocyanine green for testing liver function is 500 micrograms/kg given intravenously.

Administration in children. Doses of indocyanine green for cardiac assessment in infants and children are given under Uses and Administration, above.

Diagnostic use. Indocyanine green has been used to assess blood flow to various organs and in other haemodynamic studies. However, some methods of determination of indocyanine green clearance as a measure of liver blood flow have been questioned on the grounds that extraction of the dye by the liver is not complete as is often assumed.[1] Interindividual variability in indocyanine clearance may introduce further error.[2]

There have been reports of the use of indocyanine green to assess cerebral blood flow in children during cardiopulmonary bypass[3] and to measure plasma volume in

neonates.[4] In ophthalmology, indocyanine green angiography is used to visualise the choroidal circulation,[5,6] and as a stain during surgical repair of macular holes.[7,8]

1. Skak C, Keiding S. Methodological problems in the use of indocyanine green to estimate hepatic blood flow and ICG clearance in man. *Liver* 1987; 7: 155–62.
2. Bauer LA, *et al.* Variability of indocyanine green pharmacokinetics in healthy adults. *Clin Pharm* 1989; 8: 54–5.
3. Roberts I, *et al.* Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1993; 342: 1425.
4. Anthony MY, *et al.* Measurement of plasma volume in neonates. *Arch Dis Child* 1992; 67: 36–40.
5. Owens SL. Indocyanine green angiography. *Br J Ophthalmol* 1996; 80: 263–6.
6. Dzurinko VL, *et al.* Intravenous and indocyanine green angiography. *Optometry* 2004; 75: 743–55.
7. Rodrigues EB, *et al.* Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. *Ophthalmologica* 2005; 219: 251–62.
8. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; 89: 420–4.

Adverse Effects and Precautions

Indocyanine green is reported to be well tolerated. Anaphylaxis and urticaria have been reported. Solutions contain a small amount of sodium iodide and should be used with caution in patients hypersensitive to iodine. Clearance of indocyanine green may be altered by drugs that interfere with liver function.

References.

1. Jackson TL. Indocyanine green accused. *Br J Ophthalmol* 2005; 89: 395–6.
2. Cheng SN, *et al.* Ocular toxicity of intravitreal indocyanine green. *J Ocul Pharmacol Ther* 2005; 21: 85–93.
3. Gandorfer A, *et al.* Toxicity of indocyanine green in vitreoretinal surgery. *Dev Ophthalmol* 2008; 42: 69–81.

Hypersensitivity. A report of anaphylactoid reactions to indocyanine green in 3 patients.[1] The authors commented that of 20 reactions that had been reported 9 involved anaphylactoid shock (with 2 subsequent deaths) and 11 involved hypotension or bronchospasm; they suggested that such reactions were dose-dependent and had a non-immune mechanism.

1. Speich R, *et al.* Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med* 1988; 109: 345–6.

Pharmacokinetics

After intravenous injection indocyanine green is rapidly bound to plasma protein. It is taken up by the liver and is rapidly excreted unchanged into the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Infracyanine; *Ger.*: ICG-Pulsion; *Gr.*: ICG-Pulsion; *Hong Kong*: Diagnogreen†; *Irl.*: ICG-Pulsion; *Israel*: IC Green†; ICG-Pulsion; *Neth.*: ICG-Pulsion; *Singapore*: ICG-Pulsion; *USA*: IC Green.

Pharmacopoeial Preparations
USP 36: Indocyanine Green for Injection.

Inhibin

Inhibina; Ингибин.
CAS — 57285-09-3.

NOTE. The name inhibin has also been used as a proprietary name for hydroquinine hydrobromide (p. 2529.2).

Profile

Inhibin is a dimeric glycoprotein secreted by the testes and ovaries that suppresses secretion of follicle-stimulating hormone by the pituitary. As a member of the transforming growth factor-β family, it is also involved in mediation and regulation of many other physiological processes. Its two isoforms inhibin A and inhibin B have been widely investigated for their potential as markers of male infertility, ovarian cancer, and placental function. It has also been studied as a prognostic indicator of ovarian function in women undergoing assisted reproduction.

References.

1. Kumanov P, *et al.* Significance of inhibin in reproductive pathophysiology and current clinical applications. *Reprod Biomed Online* 2005; 10: 786–812.

Inosine *(rINN)*

Hipoxanthine riboside; Hypoxanthine Riboside; Inosina; Inosinum; Инозин.
6,9-Dihydro-9-β-D-ribofuranosyl-1*H*-purin-6-one.
$C_{10}H_{12}N_4O_5$=268.2
CAS — 58-63-9.
ATC — D06BB05; G01AX02; S01XA10.
ATC Vet — QD06BB05; QG01AX02; QS01XA10.
UNII — 5A614L51CT.

Pharmacopoeias. In *Chin.*

Profile

Inosine has been used in the treatment of anaemias and cardiovascular, liver, and skin disorders and has been used as a tonic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Jie Di Lin (安洁迪林); An Qi Mi Rui (安琪米瑞); Ba Quan (巴泉); Dan Ze (丹泽); De Yi Mei (德益美); Di Li (迪力); En Li Ke (恩立克); Fu Li Ding (复力定); Fu Li Xin (复力欣); Gan Ke (甘可); Gan Quan (甘全); Hu Yue (湖月); Ke Mi Ya (科米雅); Lai Mei Kang (莱美康); Lan Xu (兰旭); Li Fu (力孚); PiDi Gan (彼迪甘); Pu Fu (普福); Qi Pang Neng (奇方能); Quan Zhu (全助); WeiMeiJia (卫每加); Xin Feng (欣丰); Yan Luo Qi (延罗祺); Yi Rong Xin (易荣欣); Yong Rui Neng (永瑞能); Ze Bei (泽贝); Zhu Lu (竹路); Zuo He (左禾); *Rus.*: Ribonosin (Рибонозин); *Ukr.*: Riboxin (Рибоксин).

Multi-ingredient Preparations. *China*: Li Sheng Si Tai (丽生斯泰); Ying Di Te (英迪特); *Ital.*: Neo-Eparbiol; *Rus.*: Cytoflavin (Цитофлавин); Remaxol (Ремаксол); *Spain*: Nutracel; *Ukr.*: Corargin (Кораргин); Cytoflavin (Цитофлавин).

Inositol

i-Inositol; Inositoli; Inositolum; *meso*-Inositol; mio-Inozytol; myo-Inositol; myo-Inositoli; Myo-Inositolum; *myo*-Inositolum; Инозитол.
myo-Inositol.
$C_6H_{12}O_6$=180.2
CAS — 87-89-8.
ATC — A11HA07.
ATC Vet — QA11HA07.
UNII — 4L6452574G.

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

Ph. Eur. 8: (*myo*-Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in alcohol.

USNF 31: (Inositol). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Inositol, an isomer of glucose, has traditionally been considered to be a vitamin B substance although it has an uncertain status as a vitamin and a deficiency syndrome has not been identified in man. Sources of inositol include whole-grain cereals, fruits, and plants, in which it occurs as the hexaphosphate, fytic acid. It also occurs in both vegetables and meats in other forms. The usual daily intake of inositol from the diet is about 1 g. It is an ingredient of many vitamin preparations and dietary supplements, and of preparations promoted for many disorders.

Inositol appears to be involved physiologically in lipid metabolism and has been tried, with little evidence of efficacy, in disorders associated with fat transport and metabolism. It has been investigated in the treatment of depression and anxiety, in diabetic neuropathy, and in neonatal respiratory distress syndrome and retinopathy of prematurity.

Neonatal respiratory distress syndrome. Inositol supplementation has been tried in premature infants with respiratory distress syndrome (p. 1608.3). A meta-analysis[1] found that infants given inositol had improved survival and lower rates of bronchopulmonary dysplasia and retinopathy of prematurity than those given placebo.

1. Howlett A, Ohlsson A. Inositol for respiratory distress syndrome in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 19/04/06).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Inositech.

Multi-ingredient Preparations. *Arg.*: Bifena; Cistidac; Desgras Burner Fat; Desgras Piel Naranja; Ripped Max; Skin Hair & Nails; *Austral.*: Metabolift Fat Burner; Natal Plus; PM Syrin; *Braz.*: Geriavite; Metiocolin B12; Xantinon Complex; *Canad.*: Emulsi Factors; Formula 17605 Diaplex; Formula 3358†; Formula AO†; Glycopro; Lipofactors & Niacin†; Liv-Gd; Liv-Gd; Live-Rite; Nia-Plex; *Chile*: Hepabil; Tonopron Jarabe; *Fr.*: Hepagrume; *Hong Kong*: Anti-Stress Hi B Plus C†; B Complex 50; Executive Stress†; Lipochol; Mega-Antioxidant†; Super Vita Vim; Vita Stress†; *India*: Alcrin-M; Alcrin; Alphamix-BT; Cherrytone; Delphicol†; Dianuron; Diapill; Efcoben; Felicita-OD; Jetositol; Meconerv Forte; N-Care Forte; Nervijen-D; Nervz-B; Neuractin Forte; Neuroglow-B; Neurosoz-MC; *Indon.*: Carni Plus; DFM; Elkana; Fitkom; Hemaviton Energy Drink; Miniceronal†; Vidaylin L; Xanda; Zamel; Zevit Grow; *Ital.*: Hepatos B12; Konorderm; Lipoenergy; Porfirin 12; *Malaysia*: Pharmaton†; Revital; Vi-Daylin; *Mex.*: Bedoyecta; *Philipp.*: Arcostrong†; Completia†; Enerzip; K-A Plus; Optigrow; Pharmaton; Rejuvenex; Revicon Forte (Improved); *Rus.*: Prohepar (Прогепар); *S.Afr.*: Clusivol; Hepavite†; Prohep†; *Singapore*: Essentials†; NutraMX; *Spain*: Dertrase; Policolinosil; Tri Hachemina†; *Switz.*: Vitiron; *Thai.*: Lipochol; Liporon; Vita Multicap; Vitop; *UK*: Lipotropic Factors; Skin Care Nutrients; *Ukr.*: Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Vitiron (Витирон); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Advanced Ear Health Formula; Alive Once Daily Womens 50+ Ultra Potency; Amino-Cerv; Biotect Plus; Cholinoid†; Clinical Nutrients 50-Plus Men; Megavite Fruits & Veggies; One A Day Vitacraves; PowerVites; Totalday; Tyler Prenatal; *Venez.*: Hepasil; Yacriton.

Interleukins

Интерлейкины.

Profile

Interleukins are cytokines (p. 2491.2) that are thought to target leucocytes. As with other cytokines, interleukins are involved in the regulation of normal immune and inflammatory responses and have both proinflammatory and anti-inflammatory actions. Interleukins used clinically include interleukin-1 (below), interleukin-2 (p. 810.1), and aldesleukin (recombinant interleukin-2) (p. 810.1). Interleukins under investigation include interleukin-3 (p. 1155.2), ilodecakin (recombinant interleukin-10) (p. 2534.2), and edodekin alfa (recombinant interleukin-12) (p. 2534.2).

Interleukins have also been implicated in the pathogenesis of some diseases, and inhibitors of interleukins or their receptors may therefore be of therapeutic value.

Antagonists acting against interleukin receptors used clinically include anakinra (recombinant interleukin-1 receptor antagonist) (p. 21.2), basiliximab (p. 1944.1), and daclizumab (p. 1957.1), which are all interleukin-2 receptor antibodies, and tocilizumab (recombinant interleukin-6 receptor antibody) (p. 77.3) Inolimomab (p. 1959.3) is an interleukin-2 receptor antibody under investigation.

Antibodies targeting interleukins have been developed and include canakinumab (p. 34.2), a recombinant human monoclonal antibody against interleukin-1β, while those under investigation include mepolizumab (recombinant interleukin-5 antibody) (p. 1214.2) and elsilimomab (recombinant interleukin-6 antibody) (p. 2534.1).

Interleukin fusion toxins are produced by combining interleukin protein sequences with a bacterial toxin (e.g. diphtheria or pseudomonas) with the aim of inhibiting specific interleukin activity. Those under investigation include interleukin-2 fusion toxins (p. 2534.1), interleukin-4 fusion toxins, and cintredekin besudotox (p. 766.1), an interleukin-13 fusion toxin.

Soluble interleukin receptors may have therapeutic value and are also being tried therapeutically: rilonacept (p. 2604.3) is an interleukin-1 blocker used in the treatment of a group of rare inherited auto-inflammatory disorders; interleukin-4 receptor is also being investigated.

Inhibitors of cysteine protease IL-1β converting enzyme (ICE) have been investigated as a means of reducing secretion of interleukin-1β (below).

Interleukin-1

Catabolin; Endogenous Pyrogen; Haematopoietin-1; IL-1; Interleucina 1; Leucocyte Endogenous Mediator; Lymphocyte Activating Factor; Интерлейкин-1.
UNII — 8666ZWZ3E1 (Interleukin-1α); X6222612J (Interleukin-1β).

Profile

Interleukin-1 is one of several polypeptides known collectively as interleukins (above). It is produced in blood and a variety of tissues by mononuclear phagocytes involved in the complex regulation of immune responses. It enhances the immune response and has proinflammatory and pyrogenic properties. There are two distinct forms, interleukin-1α and interleukin-1β.

Interleukin-1 may also be produced by recombinant DNA technology, and human recombinant interleukin-1β has been used as an adjunct to cancer chemotherapy or radiotherapy for its haematopoietic activity. It has also been investigated for its immunotropic effects in purulent infections of the lung and ear, although it has no intrinsic antibacterial activity. Adverse effects of interleukin-1 include fever, chills, flu-like symptoms, hypotension, and pain, swelling, and erythema at the site of subcutaneous injection.

Interleukin-1 is also implicated in the pathogenesis of some diseases, particularly auto-immune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Betaleukin (Бетолейкин).

Interleukin-1 Receptor Antagonists

Antagonista del Receptor de la Interleucina 1; IL-1I; IL-1ra; Interleukin-1 Inhibitors.

Profile

Endogenous antagonists to interleukin-1 receptor block the actions of interleukin-1 (p. 2533.3) and recombinant forms have been investigated in inflammatory and immune-modulated disorders.

Anakinra (p. 21.2) is a human recombinant interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis.

Interleukin-2 Fusion Toxins

Toxinas de fusión de interleucina 2.

Profile

Interleukin-2 fusion toxin is produced by replacing the receptor binding domain of diphtheria toxin with sequences from interleukin-2, thus producing specific cytotoxicity in cells expressing the interleukin-2 receptor. The interleukin-2 fusion toxin denileukin diftitox (p. 780.2) is used in the treatment of cutaneous T-cell lymphoma. The related compound DAB_{486} interleukin-2 has also been investigated in a variety of disorders.

Interleukin-6

B-cell Stimulatory Factor-2; BSF-2; Hepatocyte-Stimulating Factor; Hybridoma Growth Factor; IFN-β_2; IL-6; Interferon-β2; Интерлейкин-6.

UNII — 92OVL9080Y.

NOTE. The name Sigosix has been used as a trade mark for atexakin alfa (human recombinant interleukin-6).

Profile

Interleukin-6 is one of several polypeptides known collectively as interleukins (p. 2533.3). It is produced by many cell types and induces differentiation of B-lymphocytes and activation of T-cells. It has proinflammatory and pyrogenic properties and is involved in the regulation of immune responses and inflammation. Interleukin-6 has also been implicated in haematopoiesis.

Atexakin alfa is human recombinant interleukin-6 that has been investigated.

Since overproduction of interleukin-6 plays a crucial role in the pathogenesis of chronic inflammatory diseases, interleukin-6 antibodies (below) and interleukin-6 receptor antagonists (p. 77.3) are being investigated or used as therapeutic agents.

Interleukin-6 Antibodies

IL-6 Antibody.

Elsilimomab *(rINN)*

Elsilimomabum; Эльсилимомаб.

Immunoglobulin G1, anti-(human interleukin 6) (mouse monoclonal B-E8 heavy chain), disulfide with mouse monoclonal B-E8 κ-chain, dimer.

CAS — 468715-71-1.

Profile

Monoclonal antibodies to interleukin-6 (above) are under investigation for the treatment of disorders including post-transplant lymphoproliferative disorders and renal cell carcinoma.

Elsilimomab is an interleukin-6 monoclonal antibody under investigation.

Interleukin-10

CSIF; Cytokine synthesis inhibitory factor; IL-10; Интерлейкин-10.

CAS — 130068-27-8.

UNII — 9SC4O216V9.

Ilodecakin *(USAN, rINN)*

Ilodecakina; Ilodécakine; Ilodecakinum; Interleukin-10 (human clone pH15C); rhIL-10; Sch-52000; Илодекакин.

CAS — 149824-15-7.

UNII — 6GY6UY4UR7.

NOTE. The names Prevascar and Tenovil have been used for ilodecakin.

Profile

Interleukin-10 is one of several polypeptides known collectively as interleukins (p. 2533.3). It regulates the differentiation and proliferation of several immune cells including T-cells and B-cells. It is postulated that it has immunostimulant as well as immunosuppressive properties; it also has anti-inflammatory actions. Interleukin-10 is under investigation for inflammatory bowel disease, malignant neoplasms, skin disorders including psoriasis and reduction of scarring, rheumatoid arthritis, hepatitis C, and organ transplantation.

Ilodecakin is a recombinant form of interleukin-10 under investigation.

References.

1. Asadullah K, *et al.* Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; 55: 241–69.
2. Braat H, *et al.* Interleukin-10-based therapy for inflammatory bowel disease. *Expert Opin Biol Ther* 2003; 3: 725–31.
3. Weiss E, *et al.* The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. *J Am Acad Dermatol* 2004; 50: 657–75.
4. Asadullah K, *et al.* Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; 3: 185–92.
5. Vicari AP, Trinchieri G. Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol Rev* 2004; 202: 223–36.
6. Mocellin S, *et al.* Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol* 2005; 78: 1043–51.
7. Mege JL, *et al.* The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006; 6: 557–69.

Interleukin-12

IL-12; Интерлейкин-12.

UNII — 02FXP10O2U (interleukin-12 human recombinant).

Edodekin Alfa *(USAN, rINN)*

Edodekina alfa; Édodékine Alfa; Edodekinum Alfa; Ro-24-7472/000; Эдодекин Альфа.

CAS — 187348-17-0.

UNII — 31Z82G8ME1.

Description. A recombinant human interleukin-12.

Profile

Interleukin-12 is one of several polypeptides known collectively as interleukins (p. 2533.3). It is produced by macrophages and dendritic cells and enhances cellular immunity through induction of the activity of interferon-γ and cytotoxic T-lymphocytes. It has been investigated for the treatment of severe infections such as mycobacterial infections; it is worthy of note that children with a rare inherited susceptibility to fatal mycobacterial infections have mutations in the interleukin-12 gene. Interleukin-12 is also under study for the treatment of various cancers, including as adenovirus-mediated gene therapy.

Edodekin alfa is human recombinant interleukin-12 under investigation for the treatment of renal cell carcinoma.

References.

1. Mazzolini G, *et al.* Gene therapy of cancer with interleukin-12. *Curr Pharm Des* 2003; 9: 1981–91.
2. Kikuchi T, *et al.* Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. *J Immunother* 2004; 27: 452–9.
3. Trudeau C, *et al.* A single administration of recombinant human interleukin-12 is associated with increased expression levels of interferon-gamma and signal transducer and activator of transcription in healthy subjects. *J Clin Pharmacol* 2005; 45: 649–58.
4. Sangro B, *et al.* Gene therapy of cancer based on interleukin 12. *Curr Gene Ther* 2005; 5: 573–81.
5. Little RF, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 2006; 107: 4650–7.

Intrinsic Factor

Antianemic Factor; Castle's Intrinsic Factor; Gastric Intrinsic Factor; Внутренне Присущий Фактор.

CAS — 9008-12-2.

Profile

Intrinsic factor, a glycoprotein secreted by the parietal glands in the stomach, is required for absorption of vitamin B_{12} in the small intestine. Deficiency in intrinsic factor leads to vitamin B_{12} deficiency disorders and pernicious anaemia.

Intrinsic factor is given orally with cyanocobalamin in the Schilling test in the differential diagnosis of pernicious anaemia (see Uses and Administration of Vitamin B_{12}, p. 2108.1). It is also included in some oral preparations containing cyanocobalamin, presumably as an aid to absorption.

Difficulty in obtaining intrinsic factor and/or radio-labelled cyanocobalamin for the original Schilling test prompted studies using a recombinant human intrinsic factor in a new vitamin B_{12} absorption test. Initial results with this recombinant form were promising.[1]

1. Hvas A-M, *et al.* The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency. *Haematologica* 2006; 91: 805–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Biosanbe; Habebion†; Hemafort; Inbion; Nichobion; Sangofer; *Philipp.*: TriHEMIC; *S. Afr.*: Autrin†; *Singapore*: Hemacaps†; *USA*: Chromagen†; Contrin; Ferotrinsic; Fetrin; Livitrinsic-f†; Pronemia Hematinic; TL Icon; TriHEMIC; Trinsicon†.

Inulin *(BAN)*

Alant Starch; Inulina; Инулин.

CAS — 9005-80-5.

UNII — JOS53KRJ01.

Pharmacopoeias. In *US*.

USP 36: (Inulin). A polysaccharide which, on hydrolysis, yields mainly fructose. A white, friable, chalk-like, amorphous, odourless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Inulin is a fructan or fructose polymer. It is used intravenously as a diagnostic agent to measure the glomerular filtration rate. Although an accurate test, it is complex to perform and is generally reserved for research purposes. Crystals of inulin may be deposited on storage of the injection; they should be dissolved by heating for not more than 15 minutes before use and the injection cooled to a suitable temperature before use.

Polyfructosan, an inulin analogue of lower average molecular weight, has been used similarly.

Inulin and related fructans, such as fructo-oligosaccharides (p. 2508.1), are a form of dietary fibre and have been used as dietary supplements, particularly for their prebiotic effects.

Pharmacokinetics

Inulin is rapidly removed from the circulation after intravenous doses but is not metabolised. A trace may be found in the bile and may cross the placenta, but it is mainly eliminated in the urine by glomerular filtration without secretion or reabsorption in the renal tubule.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Philipp.*: Fibersweet.

Multi-ingredient Preparations. *Arg.*: Invisifiber; XLS; *Chile*: Reduc-Te; Reduform-P; *Fr.*: Actyflus; Arkolevure; Cebrolux; Effadiane relipidantes; Maxi-Flore; *Ger.*: Laxatan M; *Hong Kong*: LactoGG; Lepicol; *Indon.*: Becombion Grow Syrup; *Ital.*: Cistefi; Enterolactis Duo; Enteroseven; Fibrovit; Floragermina 6; Lactolas; Naturalass; Plurilac; Serilact; Snell'it; Valcap; *Malaysia*: Probio Lact Active Formula; *Philipp.*: Culturelle With Lactobacillus GG†; *Ukr.*: Zacofalk (Закофалк); *USA*: Preorbotic.

Homoeopathic Preparations. *Neth.*: Drosinula.

Pharmacopoeial Preparations

USP 36: Inulin in Sodium Chloride Injection.

Iris Versicolor

Blue Flag; Iris Virginica; Lirio azul; Касатик Разноцветный (*Iris versicolor*); Ирис Разноцветный (*Iris versicolor*).

UNII — PYCS71247P (Iris versicolor); X43D4L3DQC (Iris versicolor root).

Profile

The rhizomes of *Iris versicolor* (Iridaceae) are used in herbal preparations for skin and gastrointestinal disorders.

Homoeopathy

Iris versicolor has been used in homoeopathic medicines under the following names: Iris; Iris ver.; Iris vers.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Weleda Hauttonikum†; *Port.*: Cephyl†; *Switz.*: Venadoron; *UK*: HRI Clear Complexion; Skin Eruptions Mixture.

Homoeopathic Preparations. *Austria*: Globuli gegen Kopfschmerzen; Iris Med Complex; Mastodynon; *Canad.*: Bioactiv N†; Chelidonium Plex†; Formula DM 210†; Hea Complex†; Headache & Migraine L77; Hyalgesic HP†; Hylands Headache; *Chile*: Bioactiv N; Lumboplex; *Cz.*: Mastodynon; *Fr.*: Neurocynesine†; Phapax; *Ger.*: Antimigren; Cefanalgin†; Cephaloplant†; Dolfin; DolorA; Inffifer N; Mastodynon; Migrane Hevert†; Migrane Hevert; Migrane-Gastreu R16; Rephalgin N; Schwoneural N; *Neth.*: Cephalite; Lymphomyosot; Mastodynon†; Neurocynesine†; Speci-chol; *Rus.*: Iris-Plus (Ирис-Плюс); Mastodynon (Мастодинон); *Switz.*: Multiplex 1; *Thai.*: Mastodynon†; *Ukr.*: Mastodynon (Мастодинон).

Isobutyl Nitrite

Изобутилнитрит.
$C_4H_9NO_2$=103.1
CAS — 542-56-3.
UNII — GW9WAB6QOM.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of isobutyl nitrite:

Aroma of men; Bolt; Bullet; Climax; Hardware; Krypt tonight; Locker room; Poppers; Quicksilver; Rush; Rush Snappers; Snappers; Thrust; White out; Whiteout.

Profile

Isobutyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p. 1540.3).

Isometheptene *(BAN, rINN)* ⊗

Isometepteno; Isométheptène; Isometheptenum; Изометептен.
1,5-Dimethylhex-4-enyl(methyl)amine; 1,5,*N*-Trimethylhex-4-enylamine.
$C_9H_{19}N$=141.3
CAS — 503-01-5.
ATC — A03AX10.
ATC Vet — QA03AX10.
UNII — Y7L24THH6T.

Isometheptene Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de isometepteno; Isométheptène, Chlorhydrate d'; Isomethepteni Hydrochloridum; Изометептена гидрохлорид.
$C_9H_{19}N.HCl$=177.7
CAS — 6168-86-1.
ATC — A03AX10.
ATC Vet — QA03AX10.
UNII — 9Z4CJC3O5F.

Isometheptene Mucate *(BANM, rINNM)* ⊗

Isometepteno, mucato de; Isométheptène, Mucate d'; Isomethepteni Mucas; Mucato de isometepteno; Изометептена Мукат.
Isometheptene galactarate.
$(C_9H_{19}N)_2.C_6H_{10}O_8$=492.7
CAS — 7492-31-1.
ATC — A03AX10.
ATC Vet — QA03AX10.
UNII — 8O120FDS6P.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Isometheptene Mucate). A white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 5.4 to 6.6. Store in airtight containers. Protect from light.

USP 36: (Isometheptene Mucate). A white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 6.0 and 7.5.

Uses and Administration

Isometheptene is an indirect-acting sympathomimetic (p. 1507.3). It is included for its vasoconstrictor effect, usually as the mucate, in some analgesic combination products used to treat acute migraine attacks (p. 670.3). Typical oral doses of isometheptene mucate in migraine are 130 mg at the beginning of an attack, with 65 mg hourly thereafter as necessary, up to a total maximum dose of 325 mg in a 12-hour period.

Isometheptene hydrochloride has also been used in the management of migraine and smooth muscle spasm; it has been given orally, as well as by intramuscular, or occasionally subcutaneous, or slow intravenous, injection. The mucate has also been used in the management of muscle spasms.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3.

Interactions

As for Sympathomimetics, p. 1508.3. Isometheptene has been reported to produce severe hypertensive reactions in patients receiving MAOIs.

Bromocriptine. For a report of hypertension and life-threatening complications after use of isometheptene and *bromocriptine*, see under Sympathomimetics, p. 899.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Octinum.

Multi-ingredient Preparations. *Braz.*: Besodin; Cefaldina†; Doralgina; Dorgil; Doridina; Dorsedin; Migranette; Neosaldina; Neuralgina; Sedalgina; Sedamed; Sedol; Tensaldin; *India*: Acudrin; *UK*: Midrid; *USA*: Epidrin; Midrin; Migragesic IDA; MigraTen; Migrazone; Nodolor; Prodrin.

Pharmacopoeial Preparations

USP 36: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Isospaglumic Acid *(rINN)*

Acide Isospaglumique; Ácido Isospaglúmico; Acidum Isospaglumicum; Isospaglúmico, ácido; NAAGA; Изоспагламовая Кислота.
N-(*N*-Acetyl-L-α-aspartyl)-L-glutamic acid.
$C_{11}H_{16}N_2O_8$=304.3
CAS — 3106-85-2.
UNII — 1W8M12WXYL.

Spaglumic Acid *(rINN)*

Acide Spaglumique; Ácido espaglúmico; Acidum Spaglumicum; Спагламовая Кислота.
N-(*N*-Acetyl-L-β-aspartyl)-L-glutamic acid.
CAS — 4910-46-7.
ATC — R01AC05; S01GX03.
ATC Vet — QR01AC05; QS01GX03.
UNII — X81L78B3R8.

Profile

N-Acetyl-L-aspartylglutamate is a mast cell stabiliser and has been used as the sodium or magnesium salts of spaglumic or isospaglumic acids in eye drops for allergic eye conditions and in nasal solutions for allergic rhinitis.

N-Acetyl-L-aspartylglutamate also has a role as a neurotransmitter and has been investigated in CNS disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Naabak; *Austria*: Rhinaaxia†; *Braz.*: Naabak; Naaxia; *Chile*: Alerbak†; Naaxia†; *Fr.*: Naabak; Naaxia; Naaxiafree†; Rhinaaxia†; *Gr.*: Rhinaaxia; *Hong Kong*: Naaxia; *Hung.*: Naaxia†; *Ital.*: Naaxia; Rhinaaxia; *Philipp.*: Naaxia; *Port.*: Naabak; *Singapore*: Naabak; *Spain*: Naaxia; *Switz.*: Naabak; *Turk.*: Naaxia; *Venez.*: Naabak.

Multi-ingredient Preparations. *Gr.*: Naaxia.

Isoxsuprine Hydrochloride *(BANM, rINNM)*

Caa-40; Hidrocloruro de isoxsuprina; Isoksupriinihydrokloridi; Isoxsuprin hydrochlorid; Isoxsuprina, hidrocloruro de; Isoxsuprine, chlorhydrate d'; Isoxsuprinhydrochlorid; Isoxsuprinhydroklorid; Isoxsuprini Hydrochloridum; Izokszuprino hidrochloridas; Izoszuprin-hidroklorid; Phenoxyisopropylnorsuprifen; Изоксуприна Гидрохлорид.
1-(4-Hydroxyphenyl)-2-(1-methyl-2-phenoxyethylamino) propan-1-ol hydrochloride.
$C_{18}H_{23}NO_3.HCl$=337.8
CAS — 395-28-8 (isoxsuprine); 579-56-6 (isoxsuprine hydrochloride).
ATC — C04AA01.
ATC Vet — QC04AA01.
UNII — V74TEQ36CO.

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

Ph. Eur. 8: (Isoxsuprine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Isoxsuprine Hydrochloride). A white, odourless, crystalline powder. Soluble 1 in 500 of water, 1 in 100 of alcohol and of 0.1N sodium hydroxide solution, and 1 in 2500 of 0.1N hydrochloric acid; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 6.0. Store in airtight containers.

Uses and Administration

Isoxsuprine is a vasodilator that also stimulates beta-adrenergic receptors. It causes direct relaxation of vascular and uterine smooth muscle and its vasodilating action is greater on the arteries supplying skeletal muscles than on those supplying skin. Isoxsuprine also produces positive inotropic and chronotropic effects.

Isoxsuprine hydrochloride has been used to arrest premature labour (p. 2131.1), but drugs with a more selective action are now preferred. It has also been given in the treatment of cerebral and peripheral vascular disease.

For use as a vasodilator, isoxsuprine hydrochloride is given orally in doses of 10 to 20 mg 3 or 4 times daily.

To arrest premature labour, isoxsuprine hydrochloride is given initially by intravenous infusion in doses of 200 to 500 micrograms/minute, adjusted according to the patient's response, until control is achieved. It is now common practice to give beta agonists by syringe pump when using them to delay premature labour. Maternal blood pressure and hydration, and maternal and fetal heart rates should be monitored during the infusion. Once labour has been arrested intramuscular injections of 10 mg are given every 3 to 8 hours. $Beta_2$ agonist 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 therapy is no longer recommended in premature labour because of a lack of evidence of benefit from treatment given by these routes of administration, although prophylactic oral doses of isoxsuprine hydrochloride 30 to 90 mg daily were formerly used after parenteral therapy.

The resinate has also been used similarly.

Adverse Effects

Isoxsuprine may cause transient flushing, hypotension, tachycardia, rashes, and gastrointestinal disturbances. Maternal pulmonary oedema and fetal tachycardia have been reported after intravenous use in premature labour.

Pulmonary oedema. Pulmonary oedema has been reported in mothers given isoxsuprine for premature labour.[1,2]

1. Nagey DA, Crenshaw MC. Pulmonary complications of isoxsuprine therapy in the gravida. *Obstet Gynecol* 1982; 59 (suppl): 38S–42S.
2. Nimrod C, *et al.* Pulmonary edema associated with isoxsuprine therapy. *Am J Obstet Gynecol* 1984; 148: 625–9.

Precautions

Isoxsuprine is contra-indicated after recent arterial haemorrhage. It should not be given immediately post partum, nor should it be used for premature labour if there is infection.

In women being treated 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.

Pregnancy. Ileus was found to be more common in the offspring of mothers who received isoxsuprine than in matched controls.[1] The incidence of respiratory distress syndrome also rose as the isoxsuprine concentration in cord blood exceeded 10 nanograms/mL; likewise the incidence of hypocalcaemia and hypotension rose progressively with increasing concentrations. The cord concentrations correlated inversely with the drug-free interval before delivery and it was suggested that with frequent assessment of uterine response it should be possible to avoid delivering infants at a time when they have high plasma-isoxsuprine concentrations.[1]

In another study[2] of the association between ruptured membranes, beta-adrenergic therapy, and respiratory distress syndrome, it was found that both therapy with isoxsuprine and premature rupture of membranes were individually associated with a lowered incidence of respiratory distress syndrome, but when present together they resulted in an increased risk of respiratory distress syndrome. It was suggested that therapy with beta-adrenergic drugs including isoxsuprine should be restricted to patients with intact membranes.[1]

1. Brazy JE, *et al.* Isoxsuprine in the perinatal period II: relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. *J Pediatr* 1981; 98: 146–51.
2. Curet LB, *et al.* Association between ruptured membranes, tocolytic therapy, and respiratory distress syndrome. *Am J Obstet Gynecol* 1984; 148: 263–8.

Pharmacokinetics

Isoxsuprine hydrochloride is well absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 1 hour after an oral dose. A plasma half-life of about 1.5 hours has been reported. Isoxsuprine is excreted in the urine mainly as conjugates.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Duvadilan; Isodilan; Isotenk; Protellum†; Samaruc†; Uterine; *Braz.*: Inibina; *Gr.*: Cerebrovin; Duvadilan; *India*: Adilin; B-Prox; Cuprox; Dulovas; Duvabel; Duvadilan; Elprox; Feprox; Fisox; Idilan; Ioril; Isarin; Iscom; Isopreg; Isoriv; Isowin; Isox; Isoxsan; Myprox; *Indon.*: Duvadilan; Hystolan; Proterine; *Ital.*: Vasosuprina; *Mex.*: Vadosilan; *Philipp.*: Duvadilan; Duvaprine; Isoxilan; *Port.*: Dilum; *USA*: Vasodilan; Voxsuprine; *Venez.*: Duvadilan.

Pharmacopoeial Preparations
USP 36: Isoxsuprine Hydrochloride Injection; Isoxsuprine Hydrochloride Tablets.

Ivacaftor *(USAN, rINN)*

Ivacaftorum; VX-770; Ивакафтор.
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide.
$C_{24}H_{28}N_2O_3$=392.5
CAS — 873054-44-5.
ATC — R07AX02.
ATC Vet — QR07AX02.
UNII — 1Y740ILL1Z.

Uses and Administration

Ivacaftor is stated to be a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. It is used in the treatment of cystic fibrosis (p. 177.2) in patients aged 6 years and above who have a G551D mutation in the CFTR gene; it is not effective in those who are homozygous for the F508del mutation in the CFTR gene and has not been studied in other mutations.

The recommended oral dose of ivacaftor is 150 mg every 12 hours, to be taken with a fat-containing food. The dose should be reduced to 150 mg once daily in patients also taking a moderate inhibitor of the cytochrome P450 isoenzyme CYP3A; those taking a potent inhibitor of CYP3A should receive 150 mg twice weekly. For dosing in patients with hepatic impairment, see below.

References.
1. Accurso FJ, *et al.* Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010; 363: 1991–2003.
2. Davis PB, *et al.* Ivacaftor. *Nat Rev Drug Discov* 2012; 11: 349–50.
3. Flume PA, *et al.* VX08-770-104 Study Group. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* 2012; 142: 718–24.
4. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother* 2012; 46: 1065–75.

Administration in children. For doses of ivacaftor in children, see Uses and Administration, above.

Administration in hepatic impairment. In patients with moderate or severe hepatic impairment (Child-Pugh class B or C), the oral dose of ivacaftor should be reduced to 150 mg once daily; less frequent use may also be necessary in those with severe impairment.

Adverse Effects and Precautions

The most common adverse effects noted with ivacaftor are headache, oropharyngeal pain, upper respiratory-tract infections, nasal congestion, nasopharyngitis, abdominal pain, diarrhoea, nausea, rash, arthralgia, and dizziness.

Elevated transaminase levels have also been reported. Liver function should be measured before starting ivacaftor, and monitored during therapy (every 3 months for the first year, and annually thereafter). Ivacaftor should be stopped if levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are greater than 5 times the upper limit of normal; treatment may be restarted when levels return to normal.

Interactions

Ivacaftor is a substrate for the cytochrome P450 isoenzyme, CYP3A. Strong inducers of this isoenzyme such as rifampicin and St John's wort can significantly reduce ivacaftor levels and decrease its effectiveness; their use together is not recommended.

Conversely, moderate and potent inhibitors of CYP3A such as fluconazole and ketoconazole, respectively can significantly increase ivacaftor exposure and a reduced dose of ivacaftor may be appropriate (for further details, see Uses and Administration, above). Grapefruit juice, another CYP3A inhibitor, should be avoided during ivacaftor treatment.

Ivacaftor, itself, is a weak inhibitor of CYP3A and P-glycoprotein; caution is recommended when giving ivacaftor with other CYP3A or P-glycoprotein substrates, such as midazolam, digoxin, and tacrolimus.

Pharmacokinetics

Ivacaftor is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 4 hours after a single oral dose. Absorption is increased two- to fourfold when given with fat-containing food. Plasma protein binding is 99%. Ivacaftor is extensively metabolised, mainly by the cytochrome P450 isoenzyme CYP3A; one of its two major metabolites is considered to be pharmacologically active. About 88% of a dose is eliminated in the faeces as metabolites; a negligible amount is excreted in the urine as unchanged drug. The terminal half-life is about 12 hours.

Distribution of ivacaftor into milk has been found in studies in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Kalydeco; *Neth.*: Kalydeco; *Norw.*: Kalydeco; *UK*: Kalydeco; *USA*: Kalydeco.

Ivy

Břečťanový list (Ivy leaf); Efeu; Gebenių lapai (Ivy leaf); Hederae folium (Ivy leaf); Herba Hederae Helicis; Lierre, feuille de (Ivy leaf); Lierre Grimpant; Muratinlehti (Ivy leaf); Murgröneblad (Ivy leaf); Плющ Обыкновенный (*Hedera helix*).
ATC — R05CA12.
ATC Vet — QR05CA12.
ATC Herb — HR05WA5018 (Hedera helix *leaf*).
UNII — 4REE45G68Q (Hedera helix); *3D10KUA68M* (Hedera helix *flowering twig*); *ZP9XFG71A7* (Hedera helix *leaf*); *379040L9FW* (Hedera helix *leaf water*).

Pharmacopoeias. *Eur.* (see p. vii) includes the leaf and also a form for homoeopathic preparations.

Ph. Eur. 8: (*Ivy Leaf*; Hederae Folium). The whole or cut, dried leaves of *Hedera helix*, collected in spring and summer. It contains a minimum of 3% of hederacoside C ($C_{59}H_{94}O_{26}$ = 1221.4), calculated with reference to the dried drug. Protect from light.

Ph. Eur. 8: (Hedera Helix for Homoeopathic Preparations; Hedera Helix ad Praeparationes Homoeopathicas). The fresh, young, fully developed but not yet lignified branch of *Hedera helix*, harvested immediately before or at the beginning of flowering. Protect from light.

Profile

The dried leaves of ivy, *Hedera helix* (Araliaceae), contain saponins, and extracts are reported to have expectorant and spasmolytic actions. Ivy leaf is used for catarrh and chronic inflammation of the respiratory tract. It has also been applied externally.

Fresh ivy leaves can cause allergic contact dermatitis.

Homoeopathy

Ivy has been used in homoeopathic medicines under the following names: Hedera helix; Hedera; Hed. hel.

References.
1. Hofmann D, *et al.* Efficacy of dry extract of ivy leaves in children with bronchial asthma—a review of randomized controlled trials. *Phytomedicine* 2003; 10: 213–220.
2. Hannu T, *et al.* Occupational asthma to ivy (*Hedera helix*). *Allergy* 2008; 63: 482–3.
3. Jones JM, *et al.* Allergic contact dermatitis to English ivy (*Hedera helix*)—a case series. *Contact Dermatitis* 2009; 60: 179–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Athos; Cedric; Celit; Funclobron H; No-Tos Hedera; Qura Tos; *Austral.*: Cough Combat; *Austria*: Alpinamed; Prospan; *Braz.*: Abrilar; Fluijet; Hederax; Respiratus; *Chile*: Aeromed; Arliv; Fluidox; Heberin; Hedilar; Hiedrix; Muxelix; Sintosin; *Cz.*: Hedelix; Helixir; Prospan; *Fr.*: Activox Expectorant†; Activox Lierre; Prospan; *Ger.*: Bronchilon†; Bronchoforton†; Bronchostad Hustenloser; Drosithym Efeu Mono; Efeu; Efeusaft hysan; Gallith; Hedelix; Prospan; Sedotussin Efeu†; Sinuc†; Tuma; *Gr.*: Prospan; *Hung.*: Hedelix; Prospan; *Indon.*: Prospan; *Ital.*: Vertuss; *Malaysia*: Prospan; *Mex.*: Panoto-S; *Neth.*: Prospan; *Norw.*: Prospan; *Pol.*: Bronchopect†; Hedelix; Hederasal; Hederoin; Helical; Prospan; *Rus.*: Hedelix (Геделикс); *Singapore*: Abrilar; Antihus; Prospan; *Spain*: Abrilar†; Arkotux; Prospantus; *Swed.*: Prospan; *Switz.*: DemoPectol Junior; Prospan; Prospanex; Sanabronch; *UK*: Activox; DiaCough; *Ukr.*: Hedelix (Геделикс); Hederin (Гедерин); Pectolvan Hedera (Пектолван Плющ); Prospan (Проспан); *Venez.*: Prospan.

Multi-ingredient Preparations. *Arg.*: Athos-B; Cedric Pocket; Celu-Atlas; Expectosan Hierbas y Miel; Nio Marine; Snell Patch; Ukase Lulitis; Varisedan Gel; *Austria*: Bronchipret; *Chile*: Cellenergy; Celu-Atlas; Pectox; *Cz.*: Bronchipret Tymian a Brect'an; *Ger.*: Bronchipret; Broncholitan; *Hung.*: Bronchipret; *Indon.*: Bronchipret†; *Ital.*: Balsamina Kroner; Binfollpase; Binfonorm†; Clebolider†; Dicotuss; Flebolider; Golatux; Hederix; Linfonorm Cremagel; Wasotonal†; *Norw.*: Bronchosan†; *Pol.*: ApiHelix†; Hedelicum; PiniHelix; *Rus.*: Bronchipret (Бронхипрет); Insti (Инсти); *Singapore*: Mincifit Body Shaper; *Spain*: H Tussan†; *Switz.*: Bronchosan; Demo Elixir pectoral N†; DemoPectol; DemoPectol; DemoPectol; Drosinula; Hederix; Kernosan Elixir; Liberol Dragees contre la toux†; Liberol Sirop contre la toux†; Sirop pectoral; *Thai.*: Solvoprel†; *UK*: Bronchoforce Chesty Cough Ivy Complex; *Ukr.*: Bronchipret (Бронхипрет).

Homoeopathic Preparations. *Canad.*: Tygian†; *Cz.*: Galium; *Fr.*: Hedera Complexe No 120; Ipeca Complexe No 65; *Ger.*: Echinaject; Hewethyreon N; Monapax; *Neth.*: Drosinula; Gletar; Speci-chol.

Jamaica Dogwood

Fish Poison Bark; Piscidia.
UNII — 5BJV0P12FY.

Profile

Jamaica dogwood, the root bark of *Piscidia erythrina* (*P. piscipula*; *Ichthyomethia piscipula*) (Leguminosae), has analgesic, antispasmodic, and sedative properties. It is mainly used for insomnia due to neuralgia or nervous tension. The bark and twigs of Jamaica dogwood have been used as a fish poison.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Sleep Easy; *Fr.*: Jouvence de l'Abbe Soury; Schoum; *Ital.*: Sedatol; Sedatol; Soluzione Schoum; *Spain*: Solucion Schoum; *UK*: Anased; HRI Calm Life; Nodoff; Slumber; *Venez.*: Femendol.

Homoeopathic Preparations. *Fr.*: Slipeol†.

Java Tea

Arbatinių inkstažolių lapai; Jaavalainen tee; Intialainen munuaistee; Jávai vesetealevél; Javate; Orthosiphon; Orthosiphonblätter; Orthosiphonis folium; Ortosifón; Té de java; Trubkovcový list; Яванский чай.
ATC Herb — HG04BW5025 (Orthosiphon aristatus *herb*).
UNII — DSS8V86H3Y.

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

Ph. Eur. 8: (Java Tea). The fragmented, dried leaves and tops of stems of *Orthosiphon stamineus* (*O. aristatus*; *O. spicatus*). Protect from light.

Profile

Java tea is used in herbal medicine mainly for the treatment of urinary-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Urosiphon; *Ger.*: Ardeynephron; Carito mono; Diufluxx Mono; Diurevit Mono†; Nephronorm med; Repha Orphon; *Neth.*: Reinosan.

Multi-ingredient Preparations. *Austria*: Solubitrat†; *Fr.*: Dellova†; Santane O1; Tealine†; Teaslim†; *Ger.*: Aqualibra; BioCyst†; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Hevert-Blasen-Nieren-Tee N†; *Indon.*: Renax; Tensigard; *Ital.*: Dren'it; Linfoguard†; Lipa-

ven; Slimmer Plus; *Pol.*: Ginjal; Uromix†; *Spain*: Tealine; *Switz.*: Billfuge; Demonatur Dragees pour les reins et la vessie†; Herbaprosta-Caps N†; Tisane pour les reins et la vessie; Urinex; *Ukr.*: Urochol (Урохол)†.

Homoeopathic Preparations. *Ger.*: Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Jin Bu Huan

Uses and Administration

Jin bu huan is a traditional Chinese remedy used as a sedative and analgesic and variously stated to contain *Lycopodium serratum* or *Polygala chinensis*.

Adverse Effects

Adverse effects of jin bu huan include CNS depression and acute hepatotoxicity and have been attributed to its alkaloidal content of L-tetrahydropalmatine.

Acute hepatitis has been reported in 7 previously healthy patients after taking jin bu huan; symptoms occurred again in 2 after re-use.[1] It was noted that the content of plant material did not seem to correspond to the labelled species. Hepatitis and extreme fatigue have also been reported in 3 adults after taking jin bu huan for periods ranging from 6 days to 6 months.[2]

Accidental ingestion of jin bu huan by 3 children[2] produced profound lethargy and muscle weakness. Two of the children also developed respiratory depression and bradycardia.

1. Woolf GM, *et al.* Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med* 1994; 121: 729–35.
2. Horowitz RS, *et al.* The clinical spectrum of jin bu huan toxicity. *Arch Intern Med* 1996; 156: 899–903.

Juniper

Baccae Juniperi; Boróka tobozbogyó; Enbär; Enebro; Enebro, enano; Genièvre; Iuniperi Pseudo-fructus; Jalovcový plod; Juniper Berry; Juniper Fruit; Juniperi Fructus; Juniperi Galbulus; Juniperi Pseudo-fructus; Kadagių vaisiai; Katajanmarja; Szyszkojagoda jałowca; Wacholderbeeren; Zimbro; Можжевельник.

ATC Herb — HG04BW5016 (Juniperus communis: fruit); HA03AW5029 (Juniperus communis: fruit).

UNII — 464910T5N9 (Juniperus communis); O84B5194RL (Juniperus communis fruit).

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

Ph. Eur. 8: (Juniper; Juniperi galbulus). The dried ripe cone berry of *Juniperus communis*. It contains not less than 1% v/w of essential oil, calculated with reference to the anhydrous drug. It has a strongly aromatic odour, especially if crushed.

Profile

Juniper is the source of juniper oil (below). It has carminative, diuretic, antiseptic, and anti-inflammatory properties. It is used in herbal medicine and as a flavour in gin.

Homoeopathy

Juniper has been used in homoeopathic medicines under the following names: Juniperus communis; Juniperus communis sicc.; Juniperus communis e fructibus siccatis; Juniperus com; Junip. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Sidina.

Multi-ingredient Preparations. *Arg.*: Albion; Wunderbalsam; *Austral.*: Arthritic Pain Herbal Formula 1†; PMT-Eze†; *Austria*: Mariazeller; St Bonifatius-Tee†; *Canad.*: Diurenat†; Diuretic Formula; Diuretic Tablets; Herbal Diuretic†; Herbal Diuretic; Herbal Laxative plus Yogurt†; Stomach Ease; *Fr.*: Alpha Renol; Depuratum; Diatisan†; Urotisan†; *Ger.*: Amara-Tropfen; *Hung.*: Antipoll; *Ital.*: Broncosedina; Broncosedina; *Pol.*: Cholesol; *Rus.*: Diureticae Species No2 (Мочегонный Сбор 2); *S.Afr.*: Amara†; *Switz.*: Gouttes Amara; Kernosan Heidelberger Poudre; Metabol; Tisane pour les reins et la vessie; *UK*: Backache; Watershed; *Ukr.*: Uro-Control (Уро-Контрол); *USA*: Cardiopress.

Homoeopathic Preparations. *Canad.*: Amaratopfen†; Nixotinex; *Fr.*: Juniperus Complexe No 6; Poconeol no 44; *Ger.*: HanoNephrin; Levisticum S; Magen-Darm-Entoxin N; Magen-Darm-tropfen N; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Solidago Hevert Complex; *Neth.*: Chavita 2; Phonix Solidago comp.

Juniper Oil

Aceite de bayas de enebro; Borókaolaj; Enbärsolja; Enebro, aceite esencial de; Essence de Genièvre; Genièvre, huile essentielle de; Juniperi aetheroleum; Jalovcová silice; Juniper Berry Oil; Juniperi Aetheroleum; Juniperi Etheroleum; Kadagių eterinis aliejus; Katajanmarjaöljy; Oleum Juniperi; Wacholderöl; Можжевеловое Масло.

ATC Herb — HG04BW5016 (Juniperus communis: essential oil).

UNII — YNW2QPG8YK (juniper oil); SZH16R44UY (juniper berry oil).

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

Ph. Eur. 8: (Juniper Oil; Juniperi aetheroleum). The essential oil obtained by steam distillation from the ripe, non-fermented berry cones of *Juniperus communis*. A suitable antoxidant may be added. A mobile, colourless to yellowish liquid with a characteristic odour. Store at a temperature not exceeding 25 degrees.

Profile

Juniper oil has been used as a carminative and as an ingredient of herbal remedies for urinary-tract disorders and muscle and joint pain. It is also used in aromatherapy. Prolonged use may cause gastrointestinal irritation and there may be a risk of renal damage from high doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Roleca Wacholder.

Multi-ingredient Preparations. *Austria*: Berggeist; *Belg.*: Olbas; *Braz.*: Solvobil; *Fr.*: Aromadigest†; Veino Gomenol; *Ger.*: Dolocyl†; Kneipp Rheumabad Spezial†; Olbas; Weleda Bronchialbalsam; *Irl.*: Olbas; Olbas; *Ital.*: Flodolor; *Neth.*: Olbas†; *Pol.*: Analgol; Olbas; Olbas; Pinimentol; Pulmonil; *S.Afr.*: Oleum Salviae Comp†; *Singapore*: Mincifit Hodeol; *Spain*: Emolytar†; Polytar†; *Switz.*: Echinarom; Huile Po-Ho A. Vogel; Liberol Baby N; Olbas; Olbas; Spagyrom; Wiewohl†; Ziegella†; *UK*: Diuretabs; HealthAid Boldo-Plus; Olbas for Children; Olbas; Olbas; Sciargo; St Johnswort Compound.

Kallidinogenase *(BAN, rINN)*

Calicreína; Callicrein; EC 3.4.21.35; Kalidinogenasa; Kalléone; Kallidinogenaasi; Kallidinogenas; Kallidinogénase; Kallidinogenasum; Kallikrein; Каллидиногеназа.

CAS — 9001-01-8.

ATC — C04AF01.

ATC Vet — QC04AF01.

Pharmacopoeias. In *Jpn.*

Profile

Kallidinogenase is an enzyme isolated from the pancreas and urine of mammals. It converts kininogen into the kinin, kallidin. Kallidinogenase has been used in male infertility (p. 2253.1) since the kallikrein-kinin system has a physiological role in the male genital tract. It also has vasodilating properties and has been used in the treatment of peripheral vascular disorders (p. 1272.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Padutin; *China*: Guangle (广乐); Kai Li Kang (凯力康); Kainike (凯妮可).

Kalmia Latifolia

American Laurel; Breitblättrige Lorbeerrose; Broad-leafed Laurel; Calico Bush; Ivybush; Lambkill; Mountain Laurel; Sheep Laurel; Spoonwood.

ATC Herb — HD11AX5001 (Kalmia latifolia: leaf).

UNII — P1SWF7DK1Y (Kalmia latifolia); 79N6542N18 (Kalmia latifolia leaf).

NOTE. The name Spoonwood has also been used for *Mallotus philippensis*. The name Laurel has been applied to a number of unrelated species, including *Kalmia latifolia*.

Profile

The leaves of *Kalmia latifolia* (*Chamaedaphne latifolia*) (Ericaceae) are used in herbal medicine in topical preparations for a variety of skin disorders. It was formerly used orally, but its use is limited by toxicity; severe poisoning can be fatal. The plant has the reputation of being poisonous to some livestock.

Homoeopathy

Kalmia latifolia has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Joint & Muscle Cream.

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Sports Ice Joint & Muscle; *Canad.*: Formula DM 210†; *Chile*: Bioactiv Z; *Fr.*: Abbe Chaupitre no 20†; Boripharm No 23; Kalmia Complexe No 18; *Ger.*: Genu-cyl L Ho-Len-Complex; HanoCor N; Hewerheum N†; Myonasan; Naranocor HM; Neuralgie-Gastreu R70; Rheuma-Hevert†; Strophanthus comp; *Neth.*: Discus comp H.

Kava

Kava-Kava; Kaea.

CAS — 500-64-1 (kawain); 495-85-2 (methysticin); 500-62-9 (yangonin).

ATC Herb — HN05BW5001 (Piper methysticum: rhizome extract); HN05CM5020 (Piper methysticum: rhizome).

UNII — 3P306S300W (Piper methysticum); BOW48CB1XP (Piper methysticum root); M832AU6HX (methysticin); R970U49V3C (yangonin).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of kava:

'ava; Ava-ava; 'awa; Grog; Intoxicating pepper; Kawa; Kawa Kawa; Lewena; Sakau; Waka; Wati; Yangona; Yaqona.

Uses and Administration

Kava is the rhizome of *Piper methysticum* (Piperaceae), a shrub indigenous to islands of the South Pacific. It contains pyrones including kawain, methysticin, and yangonin. Kava has been used in the South Pacific to produce an intoxicating beverage used for recreational purposes and during convalescence. It is reported to have sedative, skeletal muscle relaxant, and anaesthetic properties. It is given in some anxiety- and stress-related disorders. It was formerly used as an antiseptic and diuretic in inflammatory conditions of the genito-urinary tract in the form of a liquid extract. Kawain has also been used for nervous disorders and as a tonic. Preparations of kava for internal use have been withdrawn in the UK and some other western countries on account of its potential for serious hepatotoxic effects—see Adverse Effects below.

Homoeopathy

Kava has been used in homoeopathic medicines under the following names: Piper methysticum; Piper. m.; Piper meth.

General reviews.

1. Anonymous. Kava. *Lancet* 1988; ii: 258–9.
2. Pepping J. Kava: *Piper methysticum*. *Am J Health-Syst Pharm* 1999; 56: 957–60.
3. WHO. Rhizoma Piperis Methystici. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/23.html (accessed 04/02/10)
4. Sarris J, Kavanagh DJ. Kava and St. John's wort: current evidence for use in mood and anxiety disorders. *J Altern Complement Med* 2009; 15: 827–36.

Adverse Effects

A characteristic rash resembling that of pellagra occurs in some heavy consumers of kava. Extrapyramidal effects have also been reported. There have been reports of hepatotoxicity associated with kava ranging from mild changes in liver function to irreversible damage requiring liver transplantation or resulting in death.

References.

1. Anonymous. Tonga trouble. *Pharm J* 1990; 245: 288.
2. Ruze P. Kava-induced dermopathy: a niacin deficiency? *Lancet* 1990; 335: 1442–5.
3. Schelosky L, *et al.* Kava and dopamine antagonism. *J Neurol Neurosurg Psychiatry* 1995; 58: 639–40.
4. Spillane PK, *et al.* Neurological manifestations of kava intoxication. *Med J Aust* 1997; 167: 172–3.
5. Anonymous. Kava extract linked to hepatitis. *WHO Drug Inf* 2000; 14: 98.
6. Escher M, *et al.* Hepatitis associated with kava, a herbal remedy for anxiety. *BMJ* 2001; 322: 139.
7. Anonymous. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland, 1999-2002. *MMWR* 2002; 51: 1065–7. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5147a1.htm (accessed 15/07/04)
8. Stickel F, *et al.* Hepatitis induced by Kava (Piper methysticum rhizoma). *J Hepatol* 2003; 39: 62–7.
9. Clouatre DL. Kava kava: examining new reports of toxicity. *Toxicol Lett* 2004; 150: 85–96.
10. Perez J, Holmes JF. Altered mental status and ataxia secondary to acute Kava ingestion. *J Emerg Med* 2005; 28: 49–51.
11. Ulbricht C, *et al.* Safety review of kava (Piper methysticum) by the Natural Standard Research Collaboration. *Expert Opin Drug Safety* 2005; 4: 779–94.
12. Teschke R, *et al.* Kava hepatotoxicity: a European view. *N Z Med J* 2008; 121: 90–8.

Interactions

References

1. Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.). *J Ethnopharmacol* 2004; 93: 153–60.
2. Singh YN. Potential for interaction of kava and St. John's wort with drugs. *J Ethnopharmacol* 2005; 100: 108–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Ansiopax; Calmonex; Kavagren†; Kavahexal†; Kavakan; Kavamed; Kavasedon; Laitan; *Mex.*: Laikan.

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

Homoeopathic Preparations. *Austria*: Lakrima; *Ger.*: metakaveron; *Hung.*: PSY-Stabil; *Neth.*: PSY-stabil; *Switz.*: metaneuron N; metaossylen N.

Keracyanin *(rINN)*

Cyaninoside; Keracianina; Kéracyanine; Keracyaninum; Керацианин.

3-[6-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyloxy]-3′,4′,5,7-tetrahydroxyflavylium chloride.

$C_{27}H_{31}ClO_{15}$=631.0

CAS — 18719-76-1.

UNII — V0N2VM84FV.

Profile

Keracyanin is claimed to improve visual function in poor light conditions and has been given orally in vision disorders.

Keratin

CAS — 68238-35-7.

Profile

Keratin is a group of proteins found in hair, horn, nails, and similar materials. It has been used as an enteric coating for tablets. Keratin extracts and modified keratins have been investigated for use as biomaterials. Keratin preparations have also been promoted for topical and oral use in cosmetics and nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Esmalfort; Pantogar; *Ger.*: Pantovigar; *Hong Kong*: Pantogar; *Indon.*: Pantogar; *Ital.*: Biomineral 5-Alfa Shampoo; *Mex.*: Pantogar; *Rus.*: Pantovigar (Пантовигар); *Singapore*: Pantogar; *Switz.*: Pantogar; *Turk.*: Pantogar; *Ukr.*: Pantogar (Пантогар).

Keratinase ⊗

Queratinasa; Кератиназа.

CAS — 9025-41-6.

Profile

Keratinase is a proteolytic enzyme that has been obtained from cultures of *Streptomyces fradiae*. It can digest keratin, which is resistant to most proteolytic enzymes, in the presence of trace amounts of metal ions. It is used in the commercial separation of hair from animal hides, and has been tried as a depilatory; it has also been included in some topical antibacterial ointments, presumably to aid penetration of the active substances.

Khellin *(rINN)*

Kelina; Khellipe; Khellinum; Visammin; Келлин.

4,9-Dimethoxy-7-methyl-5*H*-furo[3,2-*g*]chromen-5-one.

$C_{14}H_{12}O_5$=260.2

CAS — 82-02-0.

UNII — 5G1.17T0TJZ.

Profile

Khellin is a vasodilator obtained from *Ammi visnaga* fruit (p. 2441.2) or by synthesis and has been used in angina pectoris. It also has a bronchodilatory action and has been used in asthma. Khellin has also been tried in conjunction with UV light to treat vitiligo (see Pigmentation Disorders, p. 1687.2).

References.

1. Hofer A, *et al.* Long-term results in the treatment of vitiligo with oral khellin plus UVA. *Eur J Dermatol* 2001 11: 225–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Vicalin (Викалин); *Ukr.*: Vicalin (Викалин).

Kinkeliba

Combreti Folium; Combreto; Kinkéliba.

UNII — 02ACS1U93N (Combretum micranthum).

Pharmacopoeias. In *Fr.*

Profile

Kinkeliba is the dried leaves of *Combretum micranthum* (*C. altum*; *C. raimbaultii*) (Combretaceae), a shrub indigenous to West Africa. It has been used as an ingredient of herbal remedies given for the treatment of biliary, liver, and gastrointestinal disorders. Other species of *Combretum* are also used.

Homoeopathy

Kinkeliba has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Azema†; Hepaclem†; Jecopeptol†; Mediflor Hepatique No 5; Romarene†; Solution Stago Diluee; *Mon.*: Romarinex; *Switz.*: Bilifuge.

Klebsiella Pneumoniae Glycoprotein

Glucoproteína de Klebsiella pneumoniae; RU-41740.

Profile

Klebsiella pneumoniae glycoprotein is an immunostimulant that has been used in the management of respiratory-tract infections, wounds, and burns.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Biostim; *Cz.*: Biostim†; *Gr.*: Biostim; *Mex.*: Biostim.

Knotgrass

Knotweed; Nať rdesna ptačího; Pihatatar; Polygoni avicularis herba; Renouée des Oiseaux; Takažolių žolė; Trampgräs; Vogelknöterichkraut; Ziele rdestu ptasiego; Спорыш.

ATC Herb — HR05WA5043 (Polygonum aviculare: *herb*).

UNII — M990N03611 (Polygonum aviculare); *ZCD6009IUF* (Polygonum aviculare *top*).

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

Ph. Eur. 8: (Knotgrass; Polygoni Avicularis Herba). It consists of the whole or fragmented, dried flowering aerial parts of *Polygonum aviculare*. It contains not less than 0.3% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$=464.4) calculated with reference to the dried drug.

Profile

Knotgrass, *Polygonum aviculare* (*P. heterophyllum*) (Polygonaceae), is included in herbal preparations for mild catarrh and associated upper respiratory-tract disorders.

Homoeopathy

Knotgrass has been used in homoeopathic medicines under the following names: Polygonum aviculare.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Pulmoran; Species Urologicae Planta; *Pol.*: Cholesol; Padma 28; Reumosol; *Swed.*: Alpenkraft; *Switz.*: Arteria-vita; Padma 28; Padmed Circosan; *UK*: Padma Circosan; *Ukr.*: Ambovit (Амбовит); Phytolyt (Фитолит); Urochol (Урохол)†; Uronephron (Уронефрон); Vitokan (Витокан).

Krebiozen

Crebiocén; Кребиозен.

CAS — 9008-19-9.

Profile

Krebiozen is the name of a preparation that was formerly promoted as a 'cancer cure' in the USA, but totally discredited by the FDA. It was stated to be obtained from the blood of horses previously injected with an extract of *Actinomyces bovis*.

Kveim Antigen

Antígeno de Kveim; Антиген Квейма.

Profile

Kveim antigen is a fine suspension in physiological saline of sarcoid tissue prepared from spleens taken from patients with active sarcoidosis. It has been used as an intradermal injection in the Kveim (Kveim-Siltzbach) test for the diagnosis of sarcoidosis (p. 1612.2).

References.

1. James DG, Williams WJ. Kveim-Siltzbach test revisited. *Sarcoidosis* 1991; 8: 6–9.

The safety of the Kveim test has been questioned, particularly with reference to the risk of transmission of sarcoidosis, and of hepatitis B, HIV, and Creutzfeldt-Jakob disease.[1] However, the procedure to identify acceptable sarcoid spleens and the method of preparation were considered sufficient to reduce the risk of transmission of infections[2] and of Creutzfeldt-Jakob disease.[3]

1. Wigly RD. Moratorium on Kveim tests. *Lancet* 1993; 341: 1284.
2. du Bois RM, *et al.* Moratorium on Kveim tests. *Lancet* 1993; 342: 173.
3. de Silva RN, Will RG. Moratorium on Kveim tests. *Lancet* 1993; 342: 173.

Laburnum

Citiso; Codeso europeo; Golden Chain; Golden Rain; Laburno; Lluvia de oro; Золотой Дождь Обыкновенный.

UNII — A3V9296222 (Laburnum anagyroides).

Profile

All parts of laburnum, *Laburnum anagyroides* (*L. vulgare*; *Cytisus laburnum*) (Leguminosae), are toxic. The toxic principle is cytisine (p. 2491.1) which has actions similar to nicotine.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Cocculus Oligoplex.

Lachesis Muta

Lachesis muta; *Lachesis mutus*; South American Bushmaster; Surucucu; Лахезис мутус; Бушмейстер.

UNII — 6Y5821290C (Lachesis mutus); *V5W71SS071* (Lachesis mutus *venom*).

Profile

Lachesis muta is a venomous snake belonging to the Crotalidae family (pit vipers). It is commonly known as the South American bushmaster snake.

Homoeopathy

Lachesis muta venom has been used in homoeopathic medicines under the following names: Lachesis; Lachesis mutus.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Lymphozil†.

Homoeopathic Preparations. *Austral.*: Echine†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Respatona Sore Throat; *Austria*: Echinacea-Cosmoplex; Globuli gegen Grippe; Globuli gegen Halsweh Nr 2; Gripp Heel; Remens; Vensa; Vocara; *Canad.*: Menopause; *Chile*: Flucoccinum; Lachess; *Cz.*: Gripp Heel; Ypsiloheel; *Fr.*: Actheane; Lachesis Complexe No 122; Thlascose†; Veino-Drainol†; *Ger.*: Cefakliman H†; Cefakliman N†; Cefasept N; Cefasept†; Cefasept; Corloges; Echinacea comp; Entzundungstropfen; Femi-cyl L Ho-Len-Complex; Gelsemium Comp; Gelsemium Comp; Gripp-Heel; HanoToxin M; Hanotoxin M; Hevertotox; Hevertotox; Hovnizym HM; Infekt 1-Injektopas N; Infi-Echinacea; Influex; Jowidarmin; Klimax-Gastreu S R10; Lachemistol; Lymphaden Complex; Lymphaden Lymphdrusentabletten; Lymphaden; Lymphozil H; Miburell; Mucosa compositum; Naranotox comp; Natuimmun†; Ossidal; Pascoleucyn N; Pascoleucyn; Phonix Thuja-Lachesis spag; Pyrogenium; Schworotox A; Sinusitis Hevert SL; toxi-loges; Toxiselect; veno-loges N; Wibotin HM; Wiedimmun; Ypsiloheel N; *Hung.*: Gripp-Heel; Klimakt-Heel; *Neth.*: Emvita 10; Emvita 15; Emvita 6; Emvita 7; Gripp-Heel H; Homeocare Revito; Infragil; Klimaktolan; Klimax-Gastreu R10; Mercurius-Heel; Opsonat; *Rus.*: Climaxan (Климаксан); Klimaktoplan (Климактоплан); Remens (Ременс); Vensa (Венза); Vocara (Вокара); *S.Afr.*: Gripp-Heel; *Switz.*: Gripp-Heel; Influaforce†; Menosan†; Menstruasan; Regenaplex Nr 28a; Regenaplex Nr. 24b; Regenaplex Nr. 25c; Regenaplex Nr. 35b; Regenaplex Nr. 79; *Ukr.*: Incena (Инцена); Remens (Ременс); Vocara (Вокара); *USA*: Estrex.

Lactic Acid

Acide lactique; Acidum lacticum; E270; E326 (potassium lactate); Kwas mlekowy; Kyselina mléčná; Láctico, ácido; Laktik Asit; Maitohappo; Milchsäure; Mjölksyra; Pieno rūgštis; Tejsav; Молочная Кислота.

2-Hydroxypropionic acid; 2-hydroxypropanoic acid.

$C_3H_6O_3$=90.08.

CAS — 50-21-5; 79-33-4 ((+)-lactic acid); 10326-41-7 ((−)-lactic acid); 598-82-3 ((±)-lactic acid).

ATC — G01AD01.

ATC Vet — QG01AD01; QP53AG02.

UNII — 33X04XA5AT (lactic acid); 388D359Y7S4 (dl-lactic acid); F9S9FFU82N (l-lactic acid).

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

Eur. (see p. vii) includes monographs for the racemate and the (*S*)-enantiomer.

Ph. Eur. 8: (Lactic Acid). A mixture of lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It is usually the racemate (*RS*-lactic acid), and contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

Ph. Eur. 8: ((*S*)-Lactic Acid). A mixture of (*S*)-lactic acid, its condensation products, such as lactoyl-lactic acid and other polylactic acids, and water. The equilibrium between lactic acid and polylactic acids depends on the concentration and temperature. It contains the equivalent of 88 to 92% w/w of $C_3H_6O_3$, of which not less than 95% is the (*S*)-enantiomer. A colourless or slightly yellow, syrupy liquid. Miscible with water and with alcohol.

USP 36: (Lactic Acid). A mixture of lactic acid and lactic acid lactate equivalent to a total of 88 to 92% w/w of $C_3H_6O_3$. It is obtained by the lactic fermentation of sugars or is prepared synthetically. Lactic acid obtained by fermentation of sugars is laevorotatory, while that prepared synthetically is racemic.

A colourless or yellowish, hygroscopic, practically odourless, syrupy liquid. When it is concentrated by boiling, lactic acid lactate is formed. Miscible with water, with alcohol, and with ether; insoluble in chloroform. Store in airtight containers.

Uses and Administration

Lactic acid has actions similar to those of acetic acid (p. 2427.1) and has been used similarly in the treatment of skin and vaginal disorders. It has been used in the preparation of lactate injections and infusions to provide a source of bicarbonate for the treatment of metabolic acidosis (for the problems of using lactate in metabolic acidosis, see p. 1775.2). It is applied topically in the treatment of warts (p. 1689.3), often with salicylic acid, and in emollient creams. Other uses include the treatment of severe aphthous stomatitis in terminally ill, immunocompromised patients.

Lactic acid has also been used as a food preservative and as an ingredient of cosmetics.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1, although in the concentrations used it is less corrosive.

Neonates. There was evidence that neonates had difficulty in metabolising *R*-(-)-lactic acid and this isomer and the racemate should not be used in foods for infants less than 3 months old.[1]

1. FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications: seventeenth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 539 1974. Also available at: http://libdoc.who.int/trs/WHO_TRS_539.pdf (accessed 13/05/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lactibon; *Austria*: Espritin†; Warzin; *Belg.*: Lacta-Gynecogel; *Braz.*: Kit Rosaclean; *Canad.*: Dermalac; *Chile*: Bucerin; *China*: Lactacyd FH (令特仕); *Ger.*: KadePungin Milchsaurekur; Relactagel; *India*: Lacgel; Lactacyd; Lactal; *Irl.*: Relactagel; *Ital.*: Saugella Intilac; Unigyn; *Mex.*: Acid-Lac; Avecyde†; Lactibon; *Philipp.*: Lactacyd VG; naFlora; *Pol.*: Keratolysin†; *Spain*: Keratisdin†; *Swed.*: Calmuril; *Switz.*: Vagochyss; *UK*: Relactagel; *USA*: Lactinol; Lactrex†; *Venez.*: Dermalact; Lactibon.

Multi-ingredient Preparations. *Arg.*: Acilac; Akerat; Callicida; Callicida; Callicida; Cellskinlab C + AHA; Control Acne; Dermocridin; Duofilm; Hidrolac; Keracnyl; Lactacyd; Lacticare; Lactoplus; Muvar; Opoenterol; Oxidermos; Pasem; Punto G†; Ureadin Facial; Urecrem; Verruclean; Verrutopic; *Austral.*: Aussie Tan Skin Moisturiser†; Calmurid; Dermadrate; Dermatech Wart Treatment; Duofilm; Elucent Skin Refining Day Cream; *Austria*: Anthozym†; Calmurid; Duofilm; Helo-acid; Hemosol; Hylak forte; Hylak; Lavagin†; Prismasol; *Belg.*: Aporil; *Braz.*: Calotrat; Colpolase†; Dermacyd; Dermafree; Duofilm; Kalicid; Kalloplast; Lacticare; Lacto Vagin; Salic; Verrux; *Canad.*: Duofilm; Duoplant†; Epi-Lyt; P & S; Prismasol O; Prismasol; Prismocal; Viron Wart Lotion; *Chile*: Akerat; Biopiel; Cuidado Intimo†; Duofilm; Eucerin Higiene Intima; Bucerin Piel Grasa†; Lactacyd; Node DS†; Ureadin 30; Verrufilm; *China*: Bi Zhi Ke (比之可); Gan Bi Mei (干彼美); Lactacyd (乐特喜); Solcoderm (思可得); *Cz.*: Duofilm; Hemosol; *Denm.*: Prismasol; Verucid; *Fin.*: Calmuril; Hemosol; Prismasol Kalium; Wicnelact; *Fr.*: Akerat; Cleanance K; Duofilm; Effidigest; Geliofil; Hemosol B0; Keracnyl; Kerafilm; Lacticare†; Novophane DS; Novophane K; Prismasol; Propy-Lacticare†; Saugella Antiseptic; Saugella Antiseptic; Saugella Dermoliquide; Saugella Homme; Sebium AKN; Verrufilm; Verrupan; *Ger.*: Akaderm N†; Clabin; Duofilm; Gelifend; Solco-Derman; Vagisan; W-Tropfen; *Gr.*: Duofilm; *Hong Kong*: Collomack†; Dermadrate; Dermatech Wart Treatment; Duofilm; Eubos Feminin; Lactacyd; Mithra-Intim; Solcoderm†; Verrufilm; *Hung.*: Duofilm; Genia; *India*: Alovit-AP; Basic; Carofit; Clomic-S; Copriderm; Cotaryl; Dew Derm; Diprosis; Diprovate-MF; Duofilm; Epicort-MK; Foot Care; Gowet; Heelcare; Lobate-S; Moisturex-AP; Moisturex; Oxylac; *Indon.*: Exfoliac†; Lactacyd; Lacticare†; *Irl.*: Calmurid HC; Calmurid; Cuplex†; Duofilm; Hemosol B0; Lacticare†; Prismasol; Salactol; Salatac; *Israel*: Agisten 1; Calmurid†; Femina Lactal; Hemosol; Salatac; U-Lactin Foot Cream; U-Lactin; *Ital.*: Babygella; Bruciaporri; Decon Lavanda; Duofilm; Eudermico; Fibranorm; Gastro-Pepsin; Geliofil; Geroderm Zolfo; Ginil†; Ipso Urea; Kerafilmver; Lactacyd Derma; Lactacyd Intimo; Lactacyd Lentivo; Saugella Salviettine; Sensigel; Sensiquell; Synchrobase Duo; Thiospot; Unidermo; Vaginol; Verel; Verunec; *Malaysia*: Duofilm; Lactacyd; Lacticare; Prelactic; *Mex.*: Duofilm; Kinor; Lacticare; Rug-Derm; Urader Lactato; *Mon.*: Serelys; *Neth.*: Calmurid HC; Calmurid; Duofilm; Hemosol; Prismasol; *Norw.*: Prismasol; Verucid; *NZ*: Dermadrate†; Duofilm; *Philipp.*: Duofilm; Intima†; Kene; Lactacyd; Lacticare; Mithra-Intim; *Pol.*: ABE-Plyn; Acerin; Brodacid; Duofilm; Masc na Odciski; *Port.*: Biodin Sebo Care†; Calicida Indiano; Calmurid; Creme Laser Hidrante†; Despigmentante†; Hemosol; Pansebase Composto; Pansebase; Prismasol; Secpel Composto†; Secpel†; Ureadin Manos; Verrucare; *Rus.*: Collomac (Колломак); Duofilm (Дуофилм); Solcoderm (Солкодерм); *S. Afr.*: Duofilm; Kroko; Lacticare†; *Singapore*: Bio-Taches†; Dermadrate; Dermatech Wart Treatment; Duofilm; Lactacyd; Lacticare; Nu-Derm Exfoderm Forte; O'Yes Feminine Hygiene Wash; Octenisan; Sato Uonome Solution; U-Lactin†; *Spain*: Antiverrugas; Callicida Cor Plk†; Callix†; Ginejuvent; Keranin†; Prismasol; Unguento Callicida Naion; Verufil; *Swed.*: Hemosol; Prismasol; *Switz.*: Calmurid; Clabin; Duofilm; Hemosol B0; Prismasol; Solcoderm; Va-t'en; Waruzol; Warz-ab Extor; *Thai.*: Collomak; Duofilm; Lactacyd†; Lacticare; *Turk.*: Duoderm; *UK*: Balance Activ RX; Bazuka; Calmurid HC; Calmurid; Cuplex; Duofilm; Salactol; Salatac; *Ukr.*: Collomak (Колломак); Duofilm (Дуофилм); Solcoderm (Солкодерм); *USA*: AmLactin AP†; Epi-Lyt; Lacticare; Lactinol-E†; *Venez.*: Akerat; Collomack; Kayivis.

Homoeopathic Preparations. *Austria*: Aflubin; Metavirulent; *Canad.*: Homeo-Form P†; Sportenine; *Fr.*: Homeofortil†; Sportenine; *Ger.*: HanoOxygen E; Lactopurum†; metavirulent; Sanuvis; *Hung.*: Aflubin; *Neth.*: Sportenine†; *Rus.*: Aflubin (Афлубин); *Switz.*: Lactovis; metavirulent; Regenaplex Nr. 21c; Regenaplex Nr. 21e; *Ukr.*: Aflubin (Афлубин).

Pharmacopoeial Preparations

BP 2014: Lactic Acid Pessaries;

USP 36: Compound Clioquinol Topical Powder.

Lactobionic Acid

Acide Lactobionique; Acidum Lactobionicum; Kwas laktobionowy; Kyselina laktobionová; Lactobionsäure; Laktobionihappo; Laktobiono rūgštis; Laktobionsyra; Лактобионовая Кислота.

CAS — 96-82-2 (4-O-β-D-galactopyranosyl-gluconic acid).

UNII — 65R938S4DV.

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

Ph. Eur. 8: (Lactobionic Acid). A mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid ($C_{12}H_{22}O_{12}$ = 358.3) and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone ($C_{12}H_{20}O_{11}$ = 340.3). A white or almost white powder. Freely soluble in water; slightly soluble in anhydrous ethanol, methyl alcohol, and glacial acetic acid.

USP 36: (Lactobionic Acid). A mixture in variable proportions of 4-*O*-β-D-galactopyranosyl-D-gluconic acid and 4-*O*-β-D-galactopyranosyl-D-glucono-1,5-lactone. A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in anhydrous alcohol, in methyl alcohol, and in glacial acetic acid.

Profile

Lactobionic acid is used to form water-soluble salts of drugs such as calcium and the macrolide antibacterials clarithromycin and erythromycin. It is present, in the form of potassium lactobionate, in preservation fluids such as UW (University of Wisconsin) solution for organ transplantation; the lactobionate anion acts as an impermeant and provides an osmotic force to oppose cellular oedema in the stored organ. Lactobionic acid has similar properties to gluconic acid (p. 2515.2) and is being tried in skin care products.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: NeoStrata.

Lactoferrin

Lactotransferrin; Лактоферрин.

Profile

Lactoferrin is an iron-binding protein found in milk, saliva, and other exocrine secretions. It has antimicrobial actions and has been used in preparations for the management of dry mouth (p. 2175.3) and other mouth disorders.

Lactoferrin and other whey proteins have also been used as nutritional supplements. Recombinant forms of lactoferrin such as talactoferrin alfa (p. 860.1) are under investigation.

Reviews.

1. Marshall K. Therapeutic applications of whey protein. *Altern Med Rev* 2004; 9: 136–56.
2. Valenti P, *et al.* Lactoferrin functions: current status and perspectives. *J Clin Gastroenterol* 2004; 38 (suppl 2): S127–S129.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: BeWell†; Immune Boost†; *Ital.*: Elleffe; Endvir Simplex.

Multi-ingredient Preparations. *Austral.*: ImmunoDefence; TotalCare†; *Fr.*: Photerpes; *India*: Mvimin; *Indon.*: Bd-GARD; Laktobion; *Ital.*: Eutears; Floragermina 6; Liverton; Nepiros; Puraflor; Rivuclin; Rubrojunior; Rubrovital; Vitalmix Junior; *Singapore*: Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; *UK*: Biotene Dry Mouth; *USA*: Biotene with Calcium.

Lactoperoxidase

EC 1.11.1.7; Лактопероксидаза.

CAS — 9003-99-0.

UNII — 01UIN5OC49 (bovine lactoperoxidase).

Profile

Lactoperoxidase is a peroxidase enzyme that is present in milk and saliva. It reacts with hydrogen peroxide and thiocyanate to produce an antibacterial effect and has been used in preparations for the management of dry mouth (p. 2175.3) and other mouth disorders. It has also been used for its preservative action in cosmetics and skin-care products.

In the lactoperoxidase system for milk preservation, sodium thiocyanate and sodium percarbonate (a source of hydrogen peroxide) are added to fresh bovine milk to activate the lactoperoxidase it contains.

Reviews.

1. Kussendrager KD, van Hooijdonk AC. Lactoperoxidase: physico-chemical properties, occurrence, mechanism of action and applications. *Br J Nutr* 2000; 84 (suppl 1): S19–S25.
2. Tenovuo J. Clinical applications of antimicrobial host proteins lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. *Oral Dis* 2002; 8: 23–9.
3. Lönnerdal B. Nutritional and physiologic significance of human milk proteins. *Am J Clin Nutr* 2003; 77 (suppl): 1537S–1543S.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Flaminal; *Singapore*: Biotene†; Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; *UK*: Biotene Dry Mouth; Biotene Oralbalance; Flaminal; *USA*: Biotene with Calcium.

Laetrile

CAS — 1332-94-1 (laetrile); 29883-15-6 (amygdalin).

Profile

Laetrile is the term used for a product consisting chiefly of amygdalin, which is the major cyanogenic glycoside of apricot kernels. Amygdalin is *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosyl-β-D-glucopyranoside ($C_{20}H_{27}NO_{11}$ = 457.4). Laetrile is also used as a term for *R*-α-cyanobenzyl-6-*O*-β-D-glucopyranosiduronic acid ($C_{14}H_{15}NO_7$ = 309.3).

Laetrile was claimed to be preferentially hydrolysed in cancer cells by β-glucosidases to benzaldehyde and hydrogen cyanide, which killed the cell, but amygdalin

does not appear to be absorbed from the gastrointestinal tract, and both normal and malignant cells contain only traces of β-glucosidases. Laetrile has also been claimed to be 'vitamin B_{17}', the deficiency of which is said to result in cancer; there is no evidence for this view and laetrile is of no known value in human nutrition.

There have been several reports of cyanide poisoning and other adverse reactions associated with the use of laetrile, especially when taken orally.

A systematic review[1] concluded that data from controlled studies do not support the claims of efficacy for laetrile in cancer patients. Further references[2-4] to laetrile, including case reports[3,4] of toxic effects.

1. Milazzo S, *et al.* Laetrile treatment for cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 17/07/08).
2. Chandler RF, *et al.* Controversial laetrile. *Pharm J* 1984; **232:** 330–2.
3. Bromley J, *et al.* Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. *Ann Pharmacother* 2005; **39:** 1566–9.
4. O'Brien B, *et al.* Severe cyanide toxicity from 'vitamin supplements'. *Eur J Emerg Med* 2005; **12:** 257–8.

Laminaria

Stipites Laminariae; Styli Laminariae; Thallus Ecklioniae; Thallus Laminariae; Ламинария.
UNII — NXA595GQ1K.

Pharmacopoeias. In *Chin.*

Uses and Administration

Laminaria is the dried stalks of the seaweeds *Laminaria japonica*, *L. digitata*, and possibly other species of *Laminaria*. The stalks swell in water to about 6 times their volume and have been used surgically to dilate cavities and to dilate the cervix in labour or abortion induction.

An extract of various species of *Laminaria* has been used as a dietary supplement (see Seaweeds, Kelps, and Wracks, p. 2612.1).

References.
1. Mazouni C, *et al.* Cervical preparation with laminaria tents improves induction-to-delivery interval in second- and third-trimester medical termination of pregnancy. *Contraception* 2009; **80:** 101–4.
2. Ben-Ami I, *et al.* Safety of late second-trimester pregnancy termination by laminaria dilatation and evacuation in patients with previous multiple cesarean sections. *Am J Obstet Gynecol* 2009; **201:** 154.e1–5.

Adverse Effects

Hypersensitivity. Anaphylaxis[1-3] and toxic shock syndrome[4] have been reported after the insertion of laminaria for cervical dilatation.

1. Nguyen MT, Hoffman DR. Anaphylaxis to laminaria. *J Allergy Clin Immunol* 1995; **95:** 138–9.
2. Cole DS, Bruck LR. Anaphylaxis after laminaria insertion. *Obstet Gynecol* 2000; **95:** 1025.
3. Chanda M, *et al.* Hypersensitivity reactions following laminaria placement. *Contraception* 2000; **62:** 105–6.
4. Sutkin G, *et al.* Toxic shock syndrome after laminaria insertion. *Obstet Gynecol* 2001; **98:** 959–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Fitotranzit (Фитотранзит); Okovidit (Оковидит).

Multi-ingredient Preparations. *Fr.*: Marinol; Node DS+; *Rus.*: Evalar (Эвалар); Hyporolam (Гипоролам); Limanovit E (Лимановит Е).

Lappa

Bardana; Bardanae Radix; Bardane (Grande); Burdock; Burdock Root; Lampazo menor; Lappa Root; Лопух Лечебный.
UNII — 597E98J3Z3 (Arctium lappa root); EA541308MV (Arctium lappa fruit).

Pharmacopoeias. In *Fr.*

Chin. and *Jpn* include the fruits.

Profile

Lappa is the dried root of the great burdock, *Arctium lappa* (*A. majus*), and other species of *Arctium* (Compositae). It was formerly used in the form of a decoction as a diuretic and diaphoretic but there is little evidence of its efficacy. Herbal preparations containing lappa have been used in the treatment of skin, musculoskeletal, and gastrointestinal disorders. The leaves and fruits of *Arctium* spp. have also been used.

Homoeopathy

Lappa has been used in homoeopathic medicines under the following names: Lappa major; Lap. maj.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Philipp.*: Saforelle; *Port.*: Saforelle; *Venez.*: Saforelle.

Multi-ingredient Preparations. *Austral.*: Arctium & Zinc Compound; Burdock Complex; DermaCo; KickStart Detox; Percutane†; *Canad.*: Depuratif des Trappistes; Eliminex; Herbal Laxative†; Milk Thistle Extract Formula; Natraway Sport 1 & 2†; Natraway Sport 3†; Natural HRT; *Chile*: Capilet Locion Capilar; *Cz.*: Diabetan; *Fr.*: Arbum; Depuratif Parnel†; Mycoress; Topialyse Sensitive; Topialyse Sensitive; Zeniac LP; Zeniac; *Ger.*: Weleda Hauttonikum†; *Hong Kong*: Perfectil; *Hung.*: Depsorin; *Ital.*: Allerlux; *Jpn*: Shofusan; *Pol.*: Betasol; Immunofort; Seboren; *Port.*: Erpecalm; *Rus.*: Perfectil (Перфектил); *S.Afr.*: Lotio Pruni Comp cum Cupro†; *Singapore*: Purifying Gel; *Switz.*: Venadoron; *UK*: Aqua Ban Herbal; Aquella; Backache; Boots Water Relief; Cascade; Catarrh Mixture; Covonia Catarrh Relief; GB Tablets; Gerard House Skin; Gerard House Water Relief Tablets; HRI Clear Complexion; Modern Herbals Water Retention; Napiers Oral Skin Soother Herbal Relief; Pure Plan; Rheumatic Pain Remedy; Skin Cleansing; Skin Eruptions Mixture; Tabritis; Water Naturtabs; *Ukr.*: Perfectil (Перфектил); Vitokan (Витокан); *USA*: Detox.

Homoeopathic Preparations. *Austral.*: Echine†; *Canad.*: Adrisin†; Common Mallow Combination†; Cutisitum†; Echinacea L40†; Essigen†; Formula Homeo QR 209†; *Fr.*: Digeodren; Echinacea Complexe No 40; Homeodose 24†; Saponaria Compose; Staphysagria Complexe No 92†; *Ger.*: Regenaplex Haut G; *Switz.*: Regenaplex Nr. 80aN.

Laronidase *(USAN, rINN)*

Alpha-L-iduronidase; Aironidase; Laronidasa; Laronidasum; Laronidaz; Ларонидаз.
8-L-Histidine-α-L-iduronidase (human).
CAS — 210589-09-6.
ATC — A16AB05.
ATC Vet — QA16AB05.
UNII — WP58SVM6R4.

Uses and Administration

Laronidase is recombinant human α-L-iduronidase and is used as enzyme replacement therapy for the treatment of the non-neurological manifestations of mucopolysaccharidosis I (see below). It is given by intravenous infusion in a dose of 100 units/kg each week. The initial infusion rate should be 2 units/kg per hour, increased every 15 minutes during the first hour, as tolerated, to a maximum of 43 units/kg per hour such that the infusion is completed in about 3 to 4 hours (but see also under Adverse Effects, Treatment, and Precautions, below). In some countries, the dose is expressed as mg/kg: 100 units is equivalent to about 580 micrograms of laronidase.

Administration in children. Licensed product information for laronidase in the treatment of mucopolysaccharidosis I does not mention any specific age group, although the *BNFC* notes that the usual adult dose (see above) may be given to patients from 1 month of age.

Mucopolysaccharidosis I. Mucopolysaccharidosis I is a progressive disorder characterised by deficiency of the enzyme α-L-iduronidase, which is necessary to catalyse the hydrolysis of terminal α-L-iduronic residues of the glycosaminoglycans, dermatan sulfate and heparan sulfate. This results in their accumulation in tissues, with many clinical manifestations including hepatomegaly, skeletal abnormalities, pulmonary disease, eye disease, and progressive deterioration of the CNS. Mucopolysaccharidosis I has traditionally been classified into three main forms based on clinical symptoms and severity: Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome. Hurler syndrome is the most severe form with a life expectancy of less than 10 years. However, there is a degree of overlap between the syndromes and they are indistinguishable by routine enzyme or urine tests.

Treatment was previously limited to symptomatic management but other options to halt disease progression are now available. Haematopoietic stem-cell transplantation using bone marrow or umbilical cord blood is of benefit in systemic disease and can prevent (but not usually reverse) CNS deterioration. However, substantial adverse effects limit its use to patients with severe disease. Enzyme replacement therapy with laronidase has been reported to confer benefit on the systemic manifestations of the disease, but since it does not cross the blood-brain barrier in appreciable amounts, beneficial effect on CNS symptoms is again predicted to be unlikely. However, the improvements conferred by enzyme replacement therapy might make haematopoietic stem-cell transplantation easier to tolerate.

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11. Muenzer J, *et al.* International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. *Pediatrics* 2009; **123:** 19–29. Also available at: http://pediatrics.aappublications.org/cgi/content/full/123/1/19 (accessed 18/02/10)
12. Clarke LA, *et al.* Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. *Pediatrics* 2009; **123:** 229–40.
13. Wynn RF, *et al.* Use of enzyme replacement therapy (laronidase) before hematopoietic stem cell transplantation for mucopolysaccharidosis I: experience in 18 patients. *J Pediatr* 2009; **154:** 135–9.
14. Martins AM, *et al.* Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr* 2009; **155** (suppl 2): S32–S46.

Adverse Effects, Treatment, and Precautions

Anaphylactic and other infusion reactions, sometimes delayed in onset, have been reported in patients given laronidase and facilities for resuscitation should be available whenever it is used. Common symptoms include flushing, fever, headache, and rash. Other adverse effects commonly reported include abdominal pain, arthralgia, back pain, nausea, vomiting, diarrhoea, cough, dyspnoea, urticaria, angioedema, pruritus, chills, paraesthesia, dizziness, tachycardia, increased blood pressure, and decreased oxygen saturation. Bronchospasm, tachypnoea, cyanosis, and extravasation have also been reported. Patients with existing respiratory disease may be at risk of more severe reactions. Antihistamines and/or antipyretics (e.g. paracetamol or ibuprofen) may relieve symptoms. A reduction in the rate of infusion to half the rate at which the reaction occurred should also be considered for mild or moderate reactions; for severe reactions, the infusion should be stopped until symptoms have subsided, and then restarted at one-half to one-quarter the rate at which the reaction occurred. Adrenaline should be used with caution because there is a greater incidence of coronary artery disease in patients with mucopolysaccharidosis I. Pre-treatment with antihistamines and/or antipyretics about 60 minutes before infusion is recommended to prevent reactions. IgG antibodies to laronidase are expected to develop within 3 months of starting treatment in the majority of patients, although the effect of this on safety and efficacy is not clear. However, such patients may be at increased risk of hypersensitivity reactions and should be treated with caution. Injection site reactions have also been reported.

Interactions

Licensed product information for laronidase recommends that it should not be given with chloroquine or procaine because of the potential risk of interference with the intracellular uptake of the enzyme.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aldurazyme; *Austria*: Aldurazyme; *Belg.*: Aldurazyme; *Braz.*: Aldurazyme; *Canad.*: Aldurazyme; *Chile*: Aldurazyme; *Cz.*: Aldurazyme; *Denm.*: Aldurazyme; *Fin.*: Aldurazyme; *Fr.*: Aldurazyme; *Ger.*: Aldurazyme; *Gr.*: Aldurazyme; *Hong Kong*: Aldurazyme; *Israel*: Aldurazyme; *Ital.*: Aldurazyme; *Malaysia*: Aldurazyme; *Neth.*: Aldurazyme; *Norw.*: Aldurazyme; *NZ*: Aldurazyme; *Pol.*: Aldurazyme; *Port.*: Aldurazyme; *Spain*: Aldurazyme; *Swed.*: Aldurazyme; *Switz.*: Aldurazyme; *Thai.*: Aldurazyme; *Turk.*: Aldurazyme; *UK*: Aldurazyme; *Ukr.*: Aldurasim (Альдурезим)†; *USA*: Aldurazyme.

Laropiprant *(BAN, USAN, rINN)*

Laropiprantum; MK-0524; Ларопипрант.
[-]-[(3*R*)-4-(4-Chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta(*b*)indol-3-yl]acetic acid.
$C_{21}H_{19}ClFNO_4S$=435.9
CAS — 571170-77-9.
UNII — G7N11T8O78.

NOTE. The name Cordaptive has been used as a trade mark for a combination product of laropiprant and nicotinic acid.

Profile

Laropiprant is a prostaglandin D_2 receptor 1 antagonist that inhibits nicotinic-acid induced flushing. It has been used in a modified-release combination preparation with nicotinic acid to reduce the flushing that occurs when nicotinic acid is used in high doses for the treatment of hyperlipidaemias, but the formulation was discontinued when it was found to have no benefit over statin therapy and an increased rate of adverse effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Pelzont†.

Multi-ingredient Preparations. *Arg.*: Cordaptive; *Austria*: Pelzont†; Tredaptive†; *Belg.*: Tredaptive†; *Braz.*: Cordaptive; *Cz.*: Pelzont†; Tredaptive†; Trevaclyn†; *Denm.*: Tredaptive†; *Fr.*: Tredaptive†; *Ger.*: Tredaptive†; *Gr.*: Tredaptive†; *Hong Kong*: Tredaptive†; *Irl.*: Tredaptive†; Trevaclyn†; *Israel*: Tredaptive†; *Mex.*: Cordaptive; *Neth.*: Pelzont†; Tredaptive†; Trevaclyn†; *Norw.*: Tredaptive†; *NZ*: Tredaptive†; *Philipp.*: Tredaptive†; *Pol.*: Pelzont†; Tredaptive†; Trevaclyn†; *Port.*: Pelzont†; Tredaptive†; Trevaclyn†; *Singapore*: Tredaptive†; *Spain*: Tredaptive†; *Swed.*: Tredaptive†; *Switz.*: Tredaptive†; *UK*: Tredaptive†.

Lavender

English Lavender; Kwiat lawendy (lavender flower); Lavande, fleur de (lavender flower); Lavande, Vrai; Lavandulae flos (lavender flower); Lavendelblomma (lavender flower); Lavendelblüten; Laventelinkukka (lavender flower); Levandų žiedai (lavender flower); Levandulový květ (lavender flower); Levendulavirág (lavender flower); Лаванда Узколистная (*Lavandula angustifolia*).

ATC Herb — HN05CM5011 (Lavandula angustifolia: flower); HG048W5019 (Lavandula angustifolia: flower); HA05AW5011 (Lavandula angustifolia: flower); HA03AW5033 (Lavandula angustifolia: flower).

UNII — 9YT4B71U8P (lavender); 19AH1RAF4M (lavender extract).

Pharmacopoeias. *Eur.* (see p. vii) includes lavender flower.

Ph. Eur. 8: (Lavender Flower; Lavandulae flos). It consists of the dried flower of *Lavandula angustifolia* (*L. officinalis*). It contains not less than 1.3% v/w of essential oil, calculated with reference to the anhydrous drug. Protect from light.

Profile

Lavender flower is used as a sedative. It has also been used as a cholagogue. It is an ingredient of herbal remedies used for a variety of disorders.

Lavender flowers are the source of lavender oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Lavandula Oligoplex; *Austral.*: Cimicifuga Compound; Lavandula Compound; Tranquil Night; *Austria*: Euka; *Braz.*: Balsamo Branco; Traumac†; *Cz.*: Calmonal†; Valofyt Neo†; *Fr.*: Hepato-Solutinest†; Santane R4†; *NZ*: Botanica Hayfever; *Pol.*: Lumewal; Nervinolum; Nervinum†; Nervosol; Reumobonisol; *Port.*: Erpecalm; *S.Afr.*: Krampdruppels; *Singapore*: Stop Snoring; *Spain*: Linimento Naion; *Switz.*: Femisan; *UK*: Vital Eyes; *Ukr.*: Vitrum Beauty Elite (Витрум Бьюти Элит).

Lavender Oil

English Lavender Oil (from *L. intermedia*); Esencia de Alhucema; Esencia de Espliego; Essência de Alfazema; Foreign Lavender Oil (from *L. officinalis*); Huile Essentielle de Lavande; Lavanda, aceite esencial de; Lavande, huile essentielle de; Lavandulae aetheroleum; Lavandulae Etheroleum; Lavanta Yağı; Lavendelöl; Lavendelolja; Lavender Flower Oil; Laventeliöly; Levandų eterinis aliejus; Levandulová silice; Olejek lawendowy; Oleum Lavandulae; Лавандовое Масло.

ATC Herb — HP038X5002 (Lavandula angustifolia: essential oil); HA03AW5032 (Lavandula angustifolia: essential oil).

UNII — ZBP1YXW0H8.

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

Ph. Eur. 8: (Lavender Oil). An essential oil obtained by steam distillation from the flowering tops of *Lavandula angustifolia* (*L. officinalis*). A colourless or pale yellow clear liquid with a characteristic odour, reminiscent of linalyl acetate. Relative density 0.878 to 0.892. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Lavender oil has been used as a carminative and as a flavour. It is sometimes applied externally as an insect repellent. Its chief use is in perfumery and it is occasionally used in ointments and other pharmaceutical preparations to cover disagreeable odours. It has been suggested that lavender oil may have sedative properties after inhalation. It is also used in aromatherapy.

References.
1. Cavanagh HM, Wilkinson JM. Biological activities of lavender essential oil. *Phytother Res* 2002; 16: 301–8.

Insomnia. Ambient exposure to lavender oil produced similar sleep patterns to conventional sedatives in 4 elderly patients.[1]

1. Hardy M, *et al.* Replacement of drug treatment for insomnia by ambient odour. *Lancet* 1995; 346: 701.

Adverse Effects

Lavender oil has been reported to produce nausea, vomiting, headache, and chills when inhaled or absorbed through the skin. It may cause contact allergy and phototoxicity.

There have been reports of contact dermatitis associated with lavender oil in a shampoo,[1] and facial dermatitis after application of the oil to pillows for its sedative properties.[2] A suggestion that topical exposure to products containing lavender and melaleuca oils was associated with the development of gynaecomastia in 3 prepubertal boys,[3] was questioned by others (including manufacturers of such products).[4-7]

1. Brandão FM. Occupational allergy to lavender oil. *Contact Dermatitis* 1986; 15: 249–50.
2. Coulson IH, Khan ASA. Facial 'pillow' dermatitis due to lavender oil allergy. *Contact Dermatitis* 1999; 41: 111.
3. Henley DV, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; 356: 479–85.
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7. Dean CJ, *et al.* Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; 356: 2543.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Lasea; *Pol.*: Lawenol; *Ukr.*: Tavipec (Тавипек).

Multi-ingredient Preparations. *Arg.*: Nopucid Bio II; *Austral.*: Apex Repel Natural; Bio-Oil; Bosisto's Antiseptic Spray; Bosisto's Eucalyptus Inhalant; Bosisto's EucoSteam Inhalant; Bosisto's Nasal Inhaler; Crampeze Pain Relief; NeutraLice; Vicks Baby Balsam; *Austria*: Berggeist; Rowalind; *Belg.*: Mouskito Travel Milk†; *Braz.*: Aliviol; Benegel; Gelflex; Inhalante Yatropan; Nevrol†; *Canad.*: Amol†; Vicks Vapo Steam†; *Chile*: Migrastick; *Cz.*: Amol; Ondrejova Mast; *Fr.*: Aromasol; Arthro; Balsofumine; Dolirhume; Dystollse; Esculape†; Gouttes aux Essences; Maghora†; Paps†; Perubore; Poudre du Marcheur†; Resistim; Respirea†; Tigre de Chine; *Ger.*: Amol Heilkrautergeist N; Dolo-cyl†; Enelbin-Paste†; *Hong Kong*: Calmiderm; *Hung.*: Amol; Carmol; Inno Rheuma; Szent Lukacs; *India*: LTT Cleanser; *Indon.*: Fitajoint; *Irl.*: Massage Balm with Arnica; *Israel*: Headache Pads; *Ital.*: Citrosystem; Controller; Mistick Verde; Narhinel Balsamico Bambini; Venalta; *Malaysia*: Bio-Oil; *NZ*: Electric Blue Headlice; Electric Blue Headlice; Vicks Baby Balsam; *Pol.*: Amol; Aromatol; Carmolis; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Espol (Эспол); *S.Afr.*: Arnica Massage Oil; Entressdruppels HM; Rooilavental; *Spain*: Dolokey†; Termosan; *Switz.*: Baume du Chalet; Baume du Tigre huile; Echinarom; Oculosan; Perskindol Classic; Perskindol Classic; Pulmex; Spagyrom; Ziegella†; *Turk.*: Algo-Wax; Myo-Oil; *UK*: Arnica Massage Balm; Eucanol; Eucanol; Larch Resin comp.; Massage Balm with Calendula; Migrastick; Repelselect; *USA*: Nasal Jelly.

Homoeopathic Preparations. *Ger.*: Aurum/Lavandula comp.; *UK*: Medicinal Gargle.

Lawsone

Lawsonia; Лаусон.

2-Hydroxy-1,4-naphthoquinone.

$C_{10}H_6O_3$=174.2.

CAS — 83-72-7.

UNII — TLH4A6LV1W.

Profile

Lawsone is a dye present in henna (p. 2525.1), the leaves of *Lawsonia* spp., and may also be prepared synthetically. It has been used with dihydroxyacetone in sunscreen preparations. There appears to be no evidence that it has any sunscreening properties when used alone.

Adverse effects. Observation that lawsone causes oxidative damage to red blood cells *in vitro* supported a suggestion that percutaneous absorption of henna could contribute to unexplained neonatal hyperbilirubinaemia in countries where the ceremonial use of henna is widespread.[1]

1. Zinkham WH, Oski FA. Henna: a potential cause of oxidative hemolysis and neonatal hyperbilirubinemia. *Pediatrics* 1996; 97: 707–9.

Lead

Blei; Plomb; Piombo; Plumbum; Свинец.

Pb=207.2

CAS — 7439-92-1.

UNII — 2P299V784P.

Description. Lead is a grey, malleable and ductile metal.

Uses

Lead compounds were formerly used as astringents, but the medicinal use of preparations containing lead is no longer recommended. The lead salts or compounds that have been used have included lead acetate and lead subacetate (for lead lotion, still known sometimes as lotio plumbi), lead carbonate, lead monoxide, and lead oleate (for lead plaster-mass).

Adverse Effects

Lead poisoning (plumbism) may be due to inorganic or organic lead and may be acute or, more often, chronic. It has followed exposure to many compounds and objects from which lead may be absorbed following ingestion or inhalation. Some of those that have been incriminated include paint, pottery glazes, crystal glassware, domestic water supplies, petrol, poteen, cosmetics (particularly home-made or traditional forms such as kohl or surma), herbal or folk remedies, including traditional Chinese medicines, newsprint, and retained bullets. Children are often the victims of accidental poisoning and may be vulnerable to chronic exposure to lead from environmental pollution.

Acute effects of lead poisoning include metallic taste, abdominal pain, diarrhoea, vomiting, hypotension, muscle weakness and cramps, fatigue, abnormal liver function tests, and acute interstitial nephritis. Encephalopathy may occur and is more common in children. Symptoms of chronic poisoning with inorganic lead include anorexia, abdominal pain, constipation, anaemia, headache, fatigue, irritability, peripheral neuropathy, and encephalopathy with convulsions and coma. There may be kidney damage and impairment of mental function. Children with elevated lead concentrations may be asymptomatic apart from intellectual deficits and behavioural disorders.

Organic lead poisoning produces mainly CNS symptoms; there can be gastrointestinal and cardiovascular effects, and renal and hepatic damage.

General references to lead exposure, adverse effects, screening, and management,[1-15] and case reports of specific sources of lead exposure.[16-21]

1. WHO. Recommended health-based limits in occupational exposure to heavy metals: report of a WHO study group. *WHO Tech Rep Ser 647* 1980. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_647.pdf (accessed 08/07/08)
2. WHO. Lead—environmental aspects. *Environmental Health Criteria 85*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc85.htm (accessed 08/07/08)
3. WHO. Inorganic lead. *Environmental Health Criteria 165*. Geneva: WHO, 1995. Available at: http://www.inchem.org/documents/ehc/ehc/ehc165.htm (accessed 20/04/06)
4. Wolf AW, *et al.* Effects of iron therapy on infant blood lead levels. *J Pediatr* 2003; 143: 789–95.
5. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; 116: 1036–46.
6. Kordas K, *et al.* Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *J Pediatr* 2005; 147: 632–9.
7. Stewart WF, *et al.* Past adult lead exposure is linked to neurodegeneration measured by brain MRI. *Neurology* 2006; 66: 1476–84.
8. Zimmermann MB, *et al.* Iron fortification reduces blood lead levels in children in Bangalore, India. *Pediatrics* 2006; 117: 2014–21.
9. Téllez-Rojo MM, *et al.* Longitudinal associations between blood lead concentrations lower than 10 micrograms/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 2006; 118: e323–e330. Available at: http://pediatrics.aappublications.org/cgi/content/full/118/2/e323 (accessed 08/07/08)
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11. Menke A, *et al.* Blood lead below 0.48 micromol/L (10 micrograms/dL) and mortality among US adults. *Circulation* 2006; 114: 1388–94.
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14. Chen A, *et al.* Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? *Pediatrics* 2007; 119: e650–e658. Available at: http://pediatrics.aappublications.org/cgi/content/full/119/3/e650 (accessed 08/07/08)
15. CDC Advisory Committee on Childhood Lead Poisoning Prevention. Interpreting and managing blood lead levels <10 micrograms/dL in children and reducing childhood exposures to lead: recommendations of CDC's Advisory Committee on Childhood Lead Poisoning Prevention. *MMWR* 2007; 56 (RR-8): 1–16. Correction. *ibid.*; 56 (47): 1241. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5608a1.htm (accessed 05/08/08)
16. Powell ST, *et al.* Succimer therapy for congenital lead poisoning from maternal petrol sniffing. *Med J Aust* 2006; 184: 84–5.
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21. Berkowitz S, Tarrago R. Acute brain herniation from lead toxicity. *Pediatrics* 2006; 118: 2548–51.

Treatment of Adverse Effects

The main aim in the management of both acute and chronic lead poisoning is to control the symptoms and reduce the concentration of lead in the body. Patients should be removed from the source of exposure and iron and calcium deficiencies corrected.

Treatment of symptomatic poisoning entails supportive therapy including intravenous fluids. Renal and hepatic function should also be monitored and convulsions controlled with a benzodiazepine. Encephalopathy, which is rare in adults but more common in children, requires urgent treatment.

Acute ingestion of lead or its salts should be treated if appropriate by activated charcoal or gastric lavage if within 1 hour of ingestion of a potentially life-threatening dose. Emesis is not recommended for organic lead compounds.

In severe cases of inorganic or organic lead poisoning, chelation therapy may be required to facilitate removal of lead from the body. A lead mobilisation test that measures urinary excretion of lead after a standard dose of sodium calcium edetate (p. 1573.2) has been used as a means of assessing the need for therapy. However, because of difficulties in administering the test and uncertainties in interpreting results, some authorities have recommended blood-lead concentrations as a guide to treatment. The lead mobilisation test in addition to measurement of blood-lead concentrations may be useful in determining the necessity for chelation therapy in children (see below). Blood-lead concentrations should be obtained before starting chelation therapy, and then again after the first course since mobilisation of stored lead from body tissues may cause blood-lead concentrations to rebound after an initial drop; further courses of chelator may then be required. Raised blood-lead concentrations despite chelation therapy could also indicate continued exposure.

Blood-lead concentrations for chelation therapy and the chelating regimens used differ slightly between the UK and USA. In the UK, children with blood-lead concentrations between 10 and 50 micrograms per 100 mL are monitored but not routinely given chelation therapy, and the lead mobilisation test is no longer recommended. For blood-lead concentrations between 50 and 70 micrograms per 100 mL, oral succimer (p. 1576.3) or intravenous sodium calcium edetate (p. 1573.2) should be given. For blood-lead concentrations greater than 70 micrograms per 100 mL, intravenous sodium calcium edetate should be given. While dimercaprol (p. 1549.3) has been used in the UK, it is not currently recommended as first-line treatment for lead poisoning. In the USA, chelation therapy is not indicated for children with a blood-lead concentration less than 25 micrograms per 100 mL. Children with a blood-lead concentration of 25 to 44 micrograms per 100 mL and a positive sodium calcium edetate mobilisation test should be considered for treatment. All children with blood-lead concentrations ≥45 micrograms per 100 mL should be treated, and chelators that have been used include dimercaprol, sodium calcium edetate, penicillamine (p. 1567.1), or succimer. If encephalopathy is present, dimercaprol should be given followed 4 hours later by parenteral sodium calcium edetate.

It is considered that asymptomatic adults with a blood-lead concentration less than 50 micrograms per 100 mL and who are not pregnant do not generally require chelation therapy. However, all adults with blood-lead concentrations ≥50 micrograms per 100 mL should be considered for treatment. Those without encephalopathy may be treated with oral succimer or intravenous sodium calcium edetate; alternatives are unithiol or penicillamine. Adults with encephalopathy should be treated with parenteral sodium calcium edetate. As with children (see above), dimercaprol is given with sodium calcium edetate in the USA but not in the UK.

Lead foreign bodies may need to be removed surgically or endoscopically to prevent further exposure. Long-term management of chronic lead poisoning involves eliminating environmental lead exposure. Chelation therapy is not a substitute for environmental controls in those suffering occupational exposure.

Results from one study[1] indicated that succimer did not improve scores on tests of cognition, behaviour, or neuropsychological function despite lowering blood levels of lead in children who had initial levels of less than 45 micrograms per 100 mL. The authors suggested that, since succimer is as effective a chelator as any other currently available, chelation therapy in general may not be beneficial in children with these blood-lead levels.

1. Rogan WJ, *et al.* The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; 344: 1421–6.

Lead in the Environment

Many countries have taken action to reduce lead exposure from environmental sources, including food, paint, and petrol, by limiting or banning altogether the use of lead compounds in such sources. Such measures have been of value in reducing childhood exposure to lead. Screening of all children to detect those at risk of chronic lead poisoning and developmental deficit has been advocated, but selective screening in areas perceived as high risk may be more appropriate in countries where the overall level of lead contamination is low.

Pharmacokinetics

Lead is absorbed from the gastrointestinal tract. It is also absorbed by the lungs from dust particles or fumes.

Inorganic lead is not absorbed through intact skin, but organic lead compounds may be absorbed rapidly.

Lead is distributed in the soft tissues, with higher concentrations in the liver and kidneys. In the blood it is associated with the erythrocytes. Over a period of time lead accumulates in the body and is deposited in calcified bone, hair, and teeth. Lead crosses the placental barrier. It is excreted in the faeces, urine, and sweat, and also appears in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Vulpuran; *Mex.*: Emplasto Monopolis; *Rus.*: Teimurov (Теймуров).

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; Scleron; *Canad.*: Biomag†; Reneel†; Scleron; Travel Sickness; *Fr.*: Abbe Chaupitre no 19†; Biomag; Cocculus Complexe No 73; *Ger.*: Arnica/Betula comp; Cefadybasin SE†; Curare comp; Gelsemium Comp; Gelsemium Comp; Lobelia comp; metaginkgo†; Scleron; *Neth.*: Chavita 6; Collite; Emvita 26; *S.Afr.*: Scleron†; *Switz.*: metaginkgo; Regenaplex Nr. 25a.

Lecithin

E322; E442 (ammonium phosphatides); Lécithine; Lecithinum; Lecitina; Lesitinler; Лецитин.

CAS — 8002-43-5.

UNII — 1Z74184RGV (egg lecithin); 1DI56QDM62 (soybean lecithin).

NOTE. The term phosphatidylcholine, a synonym for phosphatidyl choline (p. 2588.3), one of the ingredients of lecithin, is also sometimes used for lecithin itself.

Pharmacopoeias. In *Ger.* Also in *USNF*.

USNF 31: (Lecithin). A complex mixture of acetone-insoluble phosphatides, which consists chiefly of phosphatidyl choline, phosphatidyl olamine, phosphatidyl serine, and phosphatidyl inositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates, as separated from the crude vegetable oil source. It contains not less than 50% of acetone-insoluble matter.

The consistency of both natural grades and refined grades of lecithin may vary from plastic to fluid, depending upon the content of free fatty acid and oil, and upon the presence or absence of other diluents. Its colour varies from light yellow to brown, depending on the source, on crop variations, and on whether it is bleached or unbleached.

It is odourless or has a characteristic, slight nutlike odour. It is partially soluble in water, but readily hydrates to form emulsions. The oil-free phosphatides are soluble in fatty acids, but are practically insoluble in fixed oils. When all phosphatide fractions are present, lecithin is partially soluble in alcohol and practically insoluble in acetone. Protect from light and from excess heat and moisture.

Profile

Lecithin is an emulsifying and stabilising agent used in both the pharmaceutical and the food industries.

Lecithin has also been used as a source of choline in the treatment of dementia (p. 388.1) but with little evidence of clinical benefit. Phosphatidyl serine (p. 2589.1) has been used similarly. Other constituents of lecithin such as phosphatidyl olamine and phosphatidyl inositol may be found in natural pulmonary surfactants (p. 2599.2).

Lecithin is also an ingredient of preparations promoted as tonics and dietary supplements in an enormous range of disorders.

References.
1. Higgins JPT, Flicker L. Lecithin for dementia and cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 17/09/09).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Herbaccion Lecitina; Reducin†; *Austral.*: Buerlecithin†; *Austria*: Buerlecithin Compact†; *Ger.*: Ocutears†; *Hung.*: Buerlecithin; *India*: Elivee; Essentiale-L; Lecivit; Livage; Livintact; *Mex.*: Lecidermt†; *Pol.*: Lecitan†; *Venez.*: Lecivar.

Multi-ingredient Preparations. *Arg.*: Ayton; Cellasene Gold; Cellasene†; Posfovita; Herbaccion Memory; KLB6 Fruit Diet; Lecitina B; No-Gras; Tanvimil Isoflavonas; Triconal; *Austral.*: Berberis Complex†; Daily Plus Max†; Extralife Arthri-Care†; Extralife Extra-Brite†; Extralife Liva-Care†; Hair Skin & Nails; Joint Ease; Natal Plus; PM Joint-Care; Vitamin E Complex; Zellulean with Escin†; *Austria*: Buerlecithin; Geriatric Pharmaton; Lecikur†; *Chile*: Bedovit Pharmaton; Biocord-E; Biocord; Cartilago T-500†; Diltotal; *Cz.*: Geriavit; *Fr.*: Magneginseng†; Neurovitol; *Ger.*: Lipidavit†; Tears Again; *Hong Kong*: Cardioace; Ginkgo-PS†; Pharmaton; Profile B Plus Fat Burner†; Slimming Aid†; Wari-Procomil†; *Hung.*: Antisklerin; Memolife; Pharmaton Vital; *India*: Lecivit-S; Mynberrys Compound; *Indon.*: Artovit; BIO-EPL†; Cholesvit; Curson†; Epatin; Hepachol; Heparsitin; Lanagogum; Lanaven Plus†; Lanavision Plus; Lecitrol; Lesichol; Lesifit; Lesipar; Letropar; Letrosil; Life 10; Lipirol; Maxivit; Neurochol; Nutriflam; Obdhamin; Oramin-G; Pharmaton Formula; Picula; Provital Plus; Vercithin; Verona; Vitachol; Vitalux; *Israel*: Pharmaton; Tears Again†; *Ital.*: Eavit Plus; Eavit; Fosfaserin; Granvit; Nutrigel; Ottovis; Solecin†; Tricortin; Valcap; Vitalux Plus; Vitalux; *Malaysia*: Livguard; Livovid; Pharmaton†; Proviton; *Mex.*: Pharmaton Complex; Pharmaton; *Philipp.*: Bio-Termin Plus with Lecithin; Heltine Plus; Homtamin-G Plus; Korgivit-E†; Leginsol-E; Liverine; Megavit; Memory DD†; Memory Plus; Memovit-E†; Multramin; Nutricap; Polynerv-E with lecithin; Premium Memori Plus; Restor-F; Rogin-E; SG-Glutergen; Vigor-ACE; Vita SL with lecithin†; Vita SL; Vitaginseng; *Pol.*: Geriavit†; Lecytyna E; Vita Buerlecithin; *Port.*: Geriso; Pansebase Composto; Pansebase; Secpel Composto†; Secpel†; *Rus.*: Geriavit (Гериавит)†; Kinder Biovital (Кидер Биовиталь); Livolin (Ливолин); *S.Afr.*: Gericomplex†; Neurotone; Pharmaton†; Vitaforce Nutri-B†; *Singapore*: Gingviton; Ginkgo-PS†; Hepasil DTX†; Neovita; Pharmaton with Selenium; Pharmaton†; Snoreeze; Vigor-Ace; Vitaton; *Switz.*: Biovital Ginseng; Pharmaton Vital Geriavit; Vita Buerlecithin; *Thal.*: Geriatric Pharmaton; Gilomax; Pharmaton; *Turk.*: Liponit; Pharmaton; *UK*: Cardioace; Episil; Kelp Plus 3; Neovita; Pharmaton; S.P.H.P.; Skin Care Nutrients; *Ukr.*: Esavit (Эсавит)†; Pitoval Shampoo (Фитовал шампунь); Hepahealth (Гепахелс); Kinder Biovital (Кидер Біовіталь); Lioliv (Лиолив)†; Lipoflavon (Липофлавон)†; Rotavit Royal (Ротавит Ройял); *USA*: Episil; KLB6; NeevoDHA; SaltStable Lo; *Venez.*: Hepasil; Lecivar Plus; Nutricap; Provax.

Homoeopathic Preparations. *Ger.*: NeyArthrosome (Revitorgan-Dilution)†; NeyGeront Vitalkapsein A.

Leishmanin

Leishmanina.

Profile

Leishmanin is a suspension of *Leishmania* promastigotes used in an intradermal test to indicate previous exposure to leishmanial antigens. Its chief use is in epidemiological studies of leishmaniasis (p. 922.1). The leishmanin skin test has also been known as the Montenegro test.

Lemon

Лимон.

UNII — 24RS0A988O.

Pharmacopoeias. *Br.* includes dried lemon peel and *Swiss* includes fresh lemon peel.

BP 2014: (Dried Lemon Peel). The dried outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus limon*. It contains not less than 2.5% v/w of volatile oil.

Profile

Lemon, *Citrus limon* (*Citrus limonum*) (Rutaceae), is an ingredient of herbal remedies used for gastrointestinal disorders and as tonics. The juice is traditionally included in preparations for colds and coughs. Lemon is a source of bioflavonoids used to improve capillary function (see Flavonoid Compounds, p. 2505.2). The peel is the source of

lemon oil (below). Citrus fruits are a source of vitamin C (p. 2110.3).

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Varicura; *Austria*: Gencydo; *Braz.*: Balsamo Branco; *Canad.*: Salusan†; *Fr.*: Amana Cellium; Anastase; *Ger.*: Gencydo; Weleda Hauttonikum†; *India*: Gludibit; *Ital.*: Flavion; *Port.*: Erpecalm; *Rus.*: Doppelherz Melissa (Допельгерц Мелисса); *Singapore*: Stop Snoring; *Switz.*: Gencydo; Venadoron.

Homoeopathic Preparations. *Fr.*: Gencydo; *UK*: Gencydo.

Pharmacopoeial Preparations
BP 2014: Concentrated Compound Gentian Infusion;
USNF 31: Lemon Tincture.

Lemon Oil

Aetheroleum Citri; Citri Etheroleum; Citrinų eterinis aliejus; Citromolaj; Citron, huile essentielle de; Citronenöl; Citronolja; Citronová silice; Esencia de Cidra; Essence de Citron; Essência de Limão; Limón, aceite esencial de; Limonis aetheroleum; Ol. Limon.; Olejek cytrynowy; Oleum Citri; Oleum Limonis; Sitruunaöljy; Лимонное Масло.
ATC Herb — HA03AW5014 (Citrus limon: essential oil).
UNII — I9GRO824LL.

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

Ph. Eur. 8: (Lemon Oil). The essential oil obtained by suitable mechanical means without the aid of heat from the fresh peel of *Citrus limon*. It contains a maximum of 0.5% β-caryophyllene, 0.5 to 2.3% geranial, 0.1 to 0.8% geranyl acetate, 56.0 to 78.0% limonene, 0.3 to 1.5% neral, 0.2 to 0.9% neryl acetate, 7.0 to 17.0% β-pinene, 1.0 to 3.0% sabinene, 6.0 to 12.0% γ-terpinene, and a maximum of 0.6% α-terpineol.

A clear mobile pale yellow to greenish-yellow liquid with a characteristic odour. It may become cloudy at low temperatures. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light. Where applicable the label should state that the contents are Italian-type lemon oil.

USNF 31: (Lemon Oil). The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus X limon* (Rutaceae), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral, is not less than 2.2% and not more than 3.8% for California-type lemon oil, and not less than 3.0% and not more than 5.5% for Italian-type lemon oil. Store in well-filled airtight containers.

Profile

Lemon oil is chiefly used in perfumery and as a flavour. It is used in the preparation of terpeneless lemon oil (below). It has also been used with other volatile agents in rubefacient preparations and preparations for respiratory-tract disorders. Both lemon oil and lemon petitgrain oils (prepared from the leaves and twigs) are used in aromatherapy.

Photosensitivity reactions and contact dermatitis have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Spasmo Claim†; *Chile*: Agua del Carmen; Agua Melisa Carminativa; *Cz.*: Amol; Coldastop; *Fr.*: Aromadetox†; Aromadigest†; Olioseptil Gorge-Larynx; Poudre du Marcheur†; *Ger.*: Amol Heilkrautergeist N; GeloSitin; Melissengeist; *Hung.*: Amol; Carmol; *Ital.*: Valda Timo e Limone; Venalta; *NZ*: Electric Blue Headlice; *Pol.*: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Aromatol; Carmolis; *Rus.*: Carmolis (Кармолис); *S.Afr.*: Balsem Vita GEEL†; Balsem Vita ROOI†; Spiritus Contra Tussim Drops†; *Swed.*: Alpenkraft; *Switz.*: DUL-X Sport; Perskindol Classic; Perskindol Classic; Pirom; Sibrovita†; Venadoron; *Turk.*: Nevrol Cemal; SH-206; *UK*: Melissa Comp.; *USA*: Mexsana.

Homoeopathic Preparations. *UK*: Cough Drops.

Pharmacopoeial Preparations
BP 2014: Aromatic Ammonia Spirit;
USNF 31: Compound Orange Spirit.

Terpeneless Lemon Oil

Limón exento de terpeno, aceite esencial de; Oleum Limonis Deterpenatum.

Pharmacopoeias. In *Br.*

BP 2014: (Terpeneless Lemon Oil). A clear colourless or pale yellow liquid, visibly free from water, with the characteristic odour and taste of lemon, prepared by concentrating lemon oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 40% w/w of aldehydes calculated as citral. Soluble 1 in 1 of alcohol (80%). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Terpeneless lemon oil is used as a flavour. It has the advantages of being stronger in taste and odour and more readily soluble than the natural oil and is used in the preparation of lemon spirit and lemon syrup.

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Lemsip Cough & Cold Dry Cough; Meltus Honey & Lemon.

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit; Lemon Spirit; Lemon Syrup.

Lemon Grass Oil

Essência de capim-Limão; Indian Melissa Oil; Indian Verbena Oil; Lemongrass, aceite de; Lemongrass Oil; Oleum Graminis Citrati; Лемонграссовое Масло.
ATC Herb — HA03AW5022 (Cymbopogon citratus: essential oil).
UNII — 5BIA40E9ED.

Profile

Lemon grass oil is the volatile oil obtained by distillation from *Cymbopogon flexuosus* or *C. citratus* (Gramineae). It contains citral (p. 2480.2) and citronellal.

Lemon grass oil was formerly given as a carminative. It has been used in perfumery and as a flavour. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Apex Repel Natural; *Canad.*: Salusan†; *Fr.*: Aromavital†; *India*: Artrex.

Lemon Verbena

Herba Lippiae Citriodorae; Herba Verbenae Odoratae; Hierba luisa; Verbenae citriodoratae folium (lemon verbena leaf); Verveine Odorante; Verveine odorante, feuille de (lemon verbena leaf); Вербена Лимонная.
UNII — 9B1F4HKA9O.

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

Ph. Eur. 8: (Lemon Verbena Leaf). The whole or fragmented, dried leaves of *Aloysia citriodora* (*A. triphylla, Verbena triphylla, Lippia citriodora*). It contains a minimum of 2.5% acteoside ($C_{29}H_{36}O_{15}$ = 624.6) expressed as ferulic acid and not less than 0.3% v/w essential oil for the whole drug and 0.2% v/w essential oil for the fragmented drug, all calculated with reference to the dried drug. After grinding it has a characteristic odour reminiscent of lemon.

Profile

Lemon verbena, the flowering tops or leaves of *Lippia citriodora* (*Aloysia triphylla; Verbena triphylla*) (Verbenaceae), has antispasmodic and sedative actions and has been used for gastrointestinal disorders and as a tonic. It is most commonly used as an ingredient of herbal teas.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Agua del Carmen.

Lentinan

LC-33; Lentinano; Лентинан.
CAS — 37339-90-5.
ATC — L03AX01.
ATC Vet — QL03AX01.
UNII — 6751655D1D.

Profile

Lentinan is a β-1,3-D-glucan extracted from the shiitake mushroom *Lentinula edodes* (*Lentinus edodes*). It appears to act as an immunostimulant and has been tried in the treatment of malignant neoplasms and in HIV infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Tian Di Xin (天地欣); *Jpn*: Lenacut.

Multi-ingredient Preparations. *USA*: Immunicare.

Lepromin

Lepromina; Лепромин.
CAS — 63163-81-5.

Profile

Lepromin is a suspension of killed *Mycobacterium leprae* prepared from the skin of heavily infected patients suffering from lepromatous leprosy (lepromin H) or from armadillo tissue infected with *M. leprae* (lepromin A). It has been used in an intradermal skin test for the classification of leprosy (p. 188.3) and the assessment of immune responsiveness to *M. leprae*. The test is not diagnostic for leprosy.

The original lepromin (of Mitsuda and Hayashi), a suspension of the whole autoclaved homogenised leproma including some tissue elements, is sometimes called integral lepromin, whereas purified bacillary suspensions are sometimes called bacillary lepromins.[1] Leprolins are the soluble proteins of the bacilli with or without proteins of the lepra, not coagulated by heating, and do not elicit the early reaction. The Dharmendra antigen is neither a lepromin nor a leprolin and is used especially for testing the early reactions; it gives only a weak late reaction. Purified protein derivatives of *Mycobacterium leprae*, such as leprosin A,[2] have also been developed.

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Leptin

Leptina; OB protein; Лептин.

Profile

Leptin, an endogenous peptide hormone produced mainly by white adipocytes in adipose tissue, is involved in the long-term maintenance of body-weight through regulation of food intake and energy expenditure. Leptin has a negative feedback effect on hypothalamic control of neurotransmitters involved in the control of appetite: thus, an increase in adipose tissue mass results in an increase in leptin concentrations that in turn suppresses expression of appetite stimulatory peptides and vice versa. Mutations of either the leptin receptor or the *ob* gene that encodes the leptin protein result in failure of leptin's control over appetite producing forms of morbid early-onset obesity. However, it is not clear that common obesity (p. 2315.1) is associated with similar genetic mutations or, as also postulated, is associated with functional leptin resistance caused by sustained high leptin concentrations.

Leptin is produced in other tissues, and studies have suggested additional functions and properties including modulation of neuroendocrine, immune, and reproductive processes. The potential role of leptin in a variety of disease states including syndromes of insulin resistance, autoimmune diseases, and cardiovascular disorders is also being studied.

Replacement therapy with recombinant leptin is under investigation in the management of obesity as well as some other disorders including generalised lipodystrophy and hypothalamic amenorrhoea secondary to energy deficits or low body-weight.

References.

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Lerdelimumab *(rINN)*

Lérdelimumab; Lerdelimumabum; Лерделимумаб.
Immunoglobulin G4, anti-(human transforming growth factor β2) (human monoclonal CAT-152 γ4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer.
CAS — 285985-06-0.

Profile

Lerdelimumab is a human monoclonal antibody specific for transforming growth factor β2 that has been investigated for the prevention of excessive postoperative scarring after glaucoma surgery.

Levomenol *(rINN)*

(-)-α-Bisabolol; Lévoménol; Levomenolum; Lewomenol; Левоменол.
(-)-6-Methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol.
$C_{15}H_{26}O$=222.4
CAS — 23089-26-1.
UNII — 24WE03BX2T.

Profile

Levomenol is a sesquiterpene isolated from the volatile oil of chamomile (p. 2474.1). It has been tried as a transepidermal penetration enhancer and is present in many emollient preparations.

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Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Aftersun; Confortel; Keracnyl; ***Austria***: Sensicutan; ***Belg.***: Purigel Crisp†; ***Chile***: Cuidado Intimo†; Effaclar H; Eucerin Higiene Intima; Eucerin Piel Grasa†; Queratopil; Ruboril; Suavigel; ***Cz.***: Sensicutan; ***Fr.***: Clean-AC; Dermophil Indien; Ephydrol; Keracnyl eau nettoyante†; Keracnyl; Seborheane†; Squaphane E; ***Ger.***: Mirfulan Spray N; Sensicutan; ***Hong Kong***: Mithra-Intim; ***Israel***: Xclair; ***Ital.***: Alcedar†; Biothymus DS; Broxo al Fluoro; Decon Lavanda; Intim; Pitiren; Resvelife; Saugella Poligyn; Tial-Z; ***Malaysia***: pH Care; ***Mex.***: Aveendix; ***Philipp.***: Mithra-Intim; Nap; ***Port.***: Hidratante VV; ***Singapore***: Bio-Taches Masque†; ***Switz.***: Antidry; Dermophil Indien; Tenderdol; ***Turk.***: Numis; ***UK***: Skin Perfecting Oil; Xclair.

Lexipafant *(BAN, USAN, rINN)*

BB-882; DO-6; Lexipafantum; Лексипафант.
Ethyl *N*-methyl-*N*-[α-(2-methylimidazo[4,5-c]pyridin-1-yl)tosyl]-L-leucinate.
$C_{23}H_{30}N_4O_4S$=458.6
CAS — 139133-26-9.
UNII — H14917M9YW.

Profile

Lexipafant is a platelet-activating factor antagonist that is being investigated in the prevention of neurological and renal complications after cardiac surgery. It has also been studied for possible applications in asthma, sepsis, and pancreatitis.

Lignin

Lignilni; Lignina; Lignin; Lignina; Ligninas; Lignine; Лигнин.
CAS — 9005-53-2.

Profile

Lignin is a polymer occurring in plant fibrous tissue; it has been reported to adsorb bile salts and acids, and has been used in the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Filtrum (Фильтрум); Polyphan (Полифан); Polyphepan (Полифепан); ***Ukr.***: Filtrum (Фильтрум)†.

Multi-ingredient Preparations. ***Rus.***: Lactofiltrum (Лактофильтрум); ***Ukr.***: Lactofiltrum-ECO (Лактофильтрум-Эко).

Linseed

Flaxseed; Leinsamen; Lenmag; Lin; Lin, graine de; Linaza; Linfrö; Linho; Lini Semen; Lini Semina; Linum; Lněné semeno; Nasienie lnu; Pellavansiemen; Semilla de Lino; Sémenys; Льняное Семя.
ATC — A06AC05.
ATC Vet — QA06AC05.
*ATC Herb — HJ01WB5009 (*Linum usitatissimum*: seed); HR05WA5023 (*Linum usitatissimum*: seed); HD02WB5005 (*Linum usitatissimum*: seed); HA06AC5007 (*Linum usitatissimum*: seed).*
UNII — 4110YT348C.

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

Ph. Eur. 8: (Linseed). The dried ripe seeds of *Linum usitatissimum*. Protect from light.

Profile

Preparations of linseed have been administered for their demulcent and laxative actions. Crushed linseed has been used as a poultice. Linseed is the source of linseed oil, below. Linseed has also been tried as a dietary supplement to improve postmenopausal symptoms, and has been investigated for its potential in reducing the risk of disorders including cardiovascular disease, diabetes mellitus, and malignant neoplasms.

General references.

1. Hall C, *et al.* Flaxseed. *Adv Food Nutr Res* 2006; 51: 1–97.
2. Basch E, *et al.* Flax and flaxseed oil (Linum usitatissimum): a review by the Natural Standard Research Collaboration. *J Soc Integr Oncol* 2007; 5: 92–105.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Canad.***: Linoforce; Optomega; ***Chile***: Aloelax; Instalax; ***Fin.***: Femarelle; ***Fr.***: Alpharegul Homme; Feminabiane Meno'Confort; ***Gr.***: Femarelle; ***Hong Kong***: Femarelle; ***India***: Femarelle; ***Israel***: Femarelle†; ***Ital.***: Lignamid; ***Mex.***: Tofupill; ***Norw.***: Femarelle; ***Pol.***: Laxantol†; Ulventroten†; ***Singapore***: Femarelle; ***Spain***: Femarelle; LinoMed; ***Swed.***: Femarelle; ***Switz.***: Linoforce; LinoMed; ***UK***: Femarelle; Linoforce; Salinum; ***USA***: Femarelle; Numoisyn.

Linseed Oil

Aceite de Linaza; Flaxseed Oil; Huile de Lin; Leinöl; Lenolaj; Lin, huile de; Linaza, aceite de; Lini Oleum; Linolja; Lněný olej; Oleum Lini; Pellavaöljy; Sémenų aliejus; Льняное Масло.
ATC — A06AC05.
ATC Vet — QA06AC05.
*ATC Herb — HD02WB5004 (*Linum usitatissimum*: oil).*
UNII — 84XB4DV00W.

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

Ph. Eur. 8: (Linseed Oil, Virgin). The oil obtained by cold expression from ripe seeds of *Linum usitatissimum*. A suitable antoxidant may be added. A clear, yellow or brownish-yellow liquid. It turns dark and gradually thickens on exposure to air. When cooled, it becomes a soft mass at about -20 degrees. Relative density about 0.931. Very slightly soluble in alcohol; miscible with petroleum spirit. Store in airtight containers. Protect from light.

Profile

Linseed oil is used in veterinary medicine as a purgative for horses and cattle. In man, linseed oil is included in topical preparations for a variety of skin disorders. It has been tried as a vegetable source of omega-3 fatty acids (p. 1460.1).

Boiled linseed oil ('boiled oil') is linseed oil heated with litharge, manganese resinate, or other driers, to a temperature of about 150 degrees so that metallic salts of the fatty acids are formed and cause the oil to dry more rapidly. It must not be used for medicinal purposes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Linna-Oil; ***Mex.***: Omelina.

Multi-ingredient Preparations. ***Austral.***: Advanced Menopause Care; Once Daily 50+ Multi; ***Austria***: Dermowund†; ***Canad.***: Prosta Ease; Pure Gardens; ***Fr.***: Kotor Articulations; Neurovitol; ***India***: Adlin; Amizox; Ankare; Arflur; Artifen-D; Artilov; Bin pain; Bioflex; Buta-Proxyvon†; Culin; Dacpar; Delaxin-M; Depain; DFO; Diclogen Plus; Dicloran-MS; Dicloriz; Diclowin Active; Dicnac Gelino; Dicnap; Difenac; Difin Plus; Dinecol; Divon; Dofec Plus; Dolobid-M; Dolopar; Dolowin; Duoflam Gel; Duoflam Spy; Elwin-Plus; Enzoflam; Pelini; Flexibel; Portafen; Gelospi; Hooky; Inflahit; Intagesic; Intragesic; Jusgo; Kloser-D; KMR; Lenex; Lenin-D; Linif; Mahadol; Medicreme-Strong; Micronac; Mobigel; Mosvar; Muscodac; Muskel; Nacmol Plus; Nacpo; Nicip Supergel; Nifgel; Noctel; Novalini; Novogel; Novonac; Nugesia; Oligel; Omni; Omnigel; Onspot; Opinac; Orthocos; Orthocure; Orthodac; Orthoris; Osteoflam; Panace; ***Ital.***: Pentaker; ***Mex.***: Optivision; ***Philipp.***: SG-Glutergen; ***Rus.***: Dicloran Plus (Диклоран Плюс); ***Spain***: Cremsol†; ***UK***: Nin Rubbing Oils; ***Ukr.***: Denebol Gel (Денебол Гель); Dicloran Plu (Диклоран Плюс); Dolaren (Доларен).

Lithium Benzoate ⊗

Litio, benzoato de.
$C_7H_5LiO_2$=128.1
CAS — 553-54-8.
UNII — R9Z042Z19E.

Profile

Lithium benzoate has been used as a diuretic and urinar disinfectant. Its use cannot be recommended because of th pharmacological effect of the lithium ion (p. 427.3). Each contains 7.8 mmol of lithium.

Homoeopathy

Lithium Benzoate has been used in homoeopathi medicines under the following names: Lithium benzoicum Lithium benz.

Lixivaptan *(USAN, rINN)* ⊗

Lixivaptán; Lixivaptanum; VPA-985; WAY-VPA-985; Ликсиваптан.
3′-Chloro-5-fluoro-4′-(5*H*-pyrrolo[2,1-c][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-o-toluanilide.
$C_{27}H_{21}ClFN_3O_2$=473.9
CAS — 168079-32-1.
UNII — 8FSX48082E.

Profile

Lixivaptan is a selective vasopressin V_2-receptor antagonist under investigation for the treatment of hyponatraemia in patients with heart failure.

References.

1. Abraham WT, *et al.* Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Hea Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol* 2006; 47: 1615–21.
2. Ku E, *et al.* Lixivaptan: a novel vasopressin receptor antagonist. *Expe Opin Invest Drugs* 2009; 18: 657–62.

Lobenzarit Sodium *(USAN, rINNM)*

CCA; Lobenzarit disódico; Lobenzarit sódico; Lobenzari Sodique; Natrii Lobenzaritum; Натрий Лобензарит.
4-Chloro-2,2′-iminodibenzoate disodium.
$C_{14}H_8ClNNa_2O_4$=335.7
CAS — 63329-53-3 (lobenzarit); 64808-48-6 (lobenzari sodium).
UNII — 7Z95P748XF.

Profile

Lobenzarit sodium has been used as an immunomodulate in rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Carfenil.

Lodoxamide *(BAN, rINN)*

Lodoksamidi; Lodoxamid; Lodoxamida; Lodoxamidum; U 42585; Лодоксамид.
N,N′-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid.
$C_{11}H_6ClN_3O_6$=311.6
CAS — 53882-12-5.
ATC — S01GX05.

ATC Vet — QS01GX05.
UNII — SPU695OD73.

Lodoxamide Ethyl *(BANM, USAN, rINNM)*

Ethylum. Lodoxamidum; Lodoxamida etilo; Lodoxamide Ethyle; U-42718; Этил Лодоксамид.
Diethyl *N,N'*-(2-Chloro-5-cyano-*m*-phenylene)dioxamate.
$C_{15}H_{14}ClN_3O_6$=367.7
CAS — 53882-13-6.
UNII — JQY1B8145B.

Lodoxamide Trometamol *(BANM, rINNM)*

Lodoksamid Trometamin; Lodoxamida trometamol; Lodoxamide Trométamol; Lodoxamide Tromethamine (USAN); Lodoxamidum Trometamolum; U-42585E; Лодоксамид Трометамол.
N,N'-(2-Chloro-5-cyano-*m*-phenylene)dioxamic acid compound with trometamol.
$C_{11}H_8ClN_3O_6.2C_4H_{11}NO_3$=553.9.
CAS — 63610-09-3.
ATC — S01GX05.
ATC Vet — QS01GX05.
UNII — 50LV9A548E.

Uses and Administration

Lodoxamide has a stabilising action on mast cells resembling that of sodium cromoglicate (p. 1225.3). Lodoxamide trometamol is used in eye drops for non-infectious allergic conjunctivitis (p. 611.1), such as vernal keratoconjunctivitis, giant papillary conjunctivitis, and allergic-atopic conjunctivitis; a concentration equivalent to 0.1% of lodoxamide is used, 1 or 2 drops usually being instilled into the eye four times daily.

Lodoxamide has also been studied for its prophylactic effect in the treatment of asthma, but has not proved to be of benefit; it has usually been given orally as the ethyl ester or by inhalation as the trometamol salt.

Conjunctivitis. Lodoxamide is an effective treatment for vernal keratoconjunctivitis.[1,2] There is some evidence that it may be more effective than sodium cromoglicate for this purpose (see Rhinitis and Conjunctivitis, p. 1227.1).

1. Anonymous. Lodoxamide for vernal keratoconjunctivitis. *Med Lett Drugs Ther* 1994; 36: 26.
2. Lee S, Allard TRFK. Lodoxamide in vernal keratoconjunctivitis. *Ann Pharmacother* 1996; 30: 535–7.

Adverse Effects

Lodoxamide eye drops may cause local irritation. Reported effects include burning or stinging, and itching. Flushing and dizziness have also been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alomide; *Austral.*: Lomide; *Belg.*: Alomide; *Braz.*: Alomide; *Canad.*: Alomide; *Chile*: Alomide†; *China*: Alomide (阿乐迈); *Cz.*: Alomide†; *Denm.*: Alomide; *Fin.*: Alomide; *Fr.*: Almide; Lodoxal†; *Ger.*: Alomide; *Gr.*: Alomide; Thilomide; *Hong Kong*: Alomide; *Hung.*: Alomide; *Indon.*: Alomide; *Irl.*: Alomide; *Israel*: Alomide; *Ital.*: Alomide; *Malaysia*: Alomide; *Mex.*: Alomide; *Norw.*: Alomide†; *NZ*: Lomide; *Philipp.*: Alconmide†; *Pol.*: Alomide; *Port.*: Alomide†; *Rus.*: Alomide (Аломид)†; *S.Afr.*: Alomide; *Singapore*: Alomide†; *Spain*: Alomide; *Thai.*: Alomide†; *Turk.*: Alomide; Thilomide; *UK*: Alomide; *Ukr.*: Alomid (Аломид); *USA*: Alomide; *Venez.*: Alomide.

Lomifylline *(rINN)*

Lomifillina; Lomifyllinum; Ломифиллин.
7-(5-Oxohexyl)theophylline.
$C_{13}H_{18}N_4O_3$=278.3
CAS — 10226-54-7.
UNII — NA91GV8GDJ.

Profile

Lomifylline is a theophylline derivative that has been used in preparations for cerebrovascular disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cervilane; Micerfin; *Braz.*: Norogil; *Chile*: Cervilane; *Mex.*: Cervilan.

Loosestrife

Blutweiderichkraut; Fackelblomster; Kyprejová nať; Lythri Herba; Purple Loosestrife; Rantakukka; Raudoklių žolė; Réti füzényű; Salicaire; Дербенник.

NOTE. Do not confuse with yellow willowherb, *Lysimachia vulgaris* which is also known as loosestrife.

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

Ph. Eur. 8: (Loosestrife; Lythri Herba). The dried flowering tops, whole or cut, of *Lythrum salicaria*. It contains not less than 5.0% of tannins, expressed as pyrogallol and calculated with reference to the dried drug. Protect from light.

Profile

Purple loosestrife, *Lythrum salicaria* (Lythraceae), is used in herbal medicine for the treatment of diarrhoea. It is also used for its astringent and antimicrobial properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Salicairine.

Multi-ingredient Preparations. *Fr.*: Saugella Dermoliquide; Saugella douceur Poligyn; *Ital.*: Gynegella P.

Lorenzo's Oil

Lorenzo, aceite de; Масло Лоренцо.

Glyceryl Trierucate

Trierucin.
1,2,3-Propanetriol tri(13-docosenoate).
$C_{69}H_{128}O_6$=1053.8
CAS — 2752-99-0.
UNII — 10IDQ0M20R.

Glyceryl Trioleate

Triolein; Триолеин.
1,2,3-Propanetriol tri(9-octandecenoate).
$C_{57}H_{104}O_6$=885.5
CAS — 122-32-7.
UNII — O05EC62663.

Profile

Lorenzo's oil is a liquid containing glyceryl trierucate (a source of erucic acid) and glyceryl trioleate (a source of oleic acid), in the ratio 1 part to 4 parts respectively. It has been used with dietary modification for the treatment of adrenoleucodystrophy, a genetic disorder characterised by demyelination, adrenal cortical insufficiency, and accumulation of saturated 'very-long-chain fatty acids'.

Adrenoleucodystrophy. Adrenoleucodystrophy is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids results in diffuse and multifocal demyelination of the nervous system and adrenocortical insufficiency. The most common form usually affects children and is characterised mainly by cerebral demyelination; it is usually fatal within a few years. In the adult variant, called adrenomyeloneuropathy, demyelination of the spinal cord and peripheral neuropathy progress slowly over many years.[1,2]

There appears to be no effective treatment for adrenoleucodystrophy or its variants. A high dietary intake of long-chain monounsaturated fatty acids, as provided by the mixture Lorenzo's oil (glyceryl trierucate with glyceryl trioleate), has been tried, the idea being to monopolise the specific enzyme involved in the conversion of long-chain fatty acids to very-long-chain fatty acids. Although dietary therapy with Lorenzo's oil has reduced plasma concentrations of saturated very-long-chain fatty acids, there is no evidence that this improves or delays progression of adrenoleucodystrophy or adrenomyeloneuropathy.[3-6] However, it has been suggested that these disorders may not respond to correction of the biochemical abnormality once neurological damage has occurred.[5] The efficacy of treatment before the appearance of neurological symptoms is currently being studied with some encouraging results.[7] There is some evidence to suggest that the childhood form may have an immunological component, but results using immunosuppressants or immunoglobulins have been reported to be disappointing.[5] Bone marrow transplants may improve symptoms but should only be tried in those with mild cerebral involvement.[1] Lovastatin can also reduce plasma concentrations of very-long-chain fatty acids.[8]

1. van Geel BM, *et al.* X linked adrenoleukodystrophy: clinical presentation, diagnosis, and therapy. *J Neurol Neurosurg Psychiatry* 1997; 63: 4–14.
2. Moser HW, *et al.* Adrenoleukodystrophy: new approaches to a neurodegenerative disease. *JAMA* 2005; 294: 3131–4.
3. Aubourg P, *et al.* A two-year trial of oleic and erucic acids ("Lorenzo's oil") as treatment for adrenomyeloneuropathy. *N Engl J Med* 1993; 329: 745–52.
4. Kaplan PW, *et al.* Visual evoked potentials in adrenoleukodystrophy: a trial with glycerol trioleate and Lorenzo oil. *Ann Neurol* 1993; 34: 169–74.
5. Rizzo WB. Lorenzo's oil—hope and disappointment. *N Engl J Med* 1993; 329: 801–2.
6. van geel BM, *et al.* Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". *J Neurol Neurosurg Psychiatry* 1999; 67: 290–9.
7. Moser HW, *et al.* Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. *Arch Neurol* 2005; 62: 1073–80.
8. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; 69: 312–22.

Adverse effects. Thrombocytopenia has been reported in patients receiving Lorenzo's oil, although patients are often asymptomatic.[1] It is possible that giant platelets which retain most of their function are produced and that these are not counted by automatic counting procedures giving a false impression of thrombocytopenia.[2]

Lymphocytopenia with an increased incidence of infection has also been reported in few patients.[3]

1. Zinkham WH, *et al.* Lorenzo's oil and thrombocytopenia in patients with adrenoleukodystrophy. *N Engl J Med* 1993; 328: 1126–7.
2. Stöckler S, *et al.* Giant platelets in erucic acid therapy for adrenoleukodystrophy. *Lancet* 1993; 341: 1414–15.
3. Unkrig CJ, *et al.* Lorenzo's oil and lymphocytopenia. *N Engl J Med* 1994; 330: 577.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: GTO Oil.

Lovage Root

Gelsvių šaknys; Korzeń lubczyka; Lestyángyökér; Levistici Radix; Levístico; Libečkový kořen; Libstickerot; Liebstöckelwurzel; Liperinjuuri; Livèche (racine de); Livèche, racine de; Корень Любистока.
UNII — 46QZ19OEX8.

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

Ph. Eur. 8: (Lovage Root). The whole or cut, dried rhizome and root of *Levisticum officinale*. The whole drug contains not less than 0.4% v/w of essential oil and the cut drug not less than 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Lovage root is used in herbal medicine for gastrointestinal and urinary-tract disorders. The leaves and seeds or fruit of lovage are used as a culinary herb and flavouring.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Ehrenhofer-Salbe; *Cz.*: Zaludecni Cajova Smes; *Fr.*: NurAiD; *Ger.*: Canephron N; Nephroselect M; *Rus.*: Canephron N (Канефрон Н); Wantong Artiplas (Ванытун Артиплас); *Switz.*: Tisane pour les reins et la vessie; *UK*: Cystipret; *Ukr.*: Canephron N (Канефрон Н); Uronephron (Уронефрон).

Homoeopathic Preparations. *Ger.*: Levisticum S; Regenaplex Haut G; *Switz.*: Regenaplex Nr. 79; *UK*: Fragador.

Luffa

Loofah; Люффа.
UNII — F0R3Y6OC6V.

Profile

Luffas are tropical and subtropical vines of the genus *Luffa* (Cucurbitaceae). The dried fibre of the fruits (luffa sponge) of *Luffa acutangula*, *L. aegyptiaca*, and *L. operculata* has traditionally been used in herbal medicine for symptoms of upper respiratory-tract disorders; the fruit pulp of some species was also used as a purgative.

The young fruits of some species are eaten as a vegetable. Luffa sponge is also used as a mildly abrasive bathing sponge.

Homoeopathy

Luffa has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Sinustrat.

Homoeopathic Preparations. *Austria*: Delufen; Erblode Heuschnupfen; Euphorbium Compositum; Globuli gegen Schnupfen

Nr 2; Globuli gegen Schnupfen Nr 3; Heuschnupfenmittel DHU†; Luffa compositum-Heel; Luffa Med Complex; Metavirulent; Rhododendroneel; *Canad.*: Euphorbium Compositum; Euphorbium Compositum; Euphorbium Compositum; Luffeel Nasal Spray; *Cz.*: Euphorbium Compositum; Luffeel; Luffeel; *Ger.*: Allergo-Loges; Allergokatt; Cefaluffa†; Euphorbium comp SN; Heuschnupfenmittel; Heuschnupfenmittel; Luffa Nasentropfen; Luffasan; Luffeel Comp; Luffeel Comp; metavirulent; Pollinosan†; Schleimhaut-Komplex I; Ho-Fu-Complex; Sinupas; Sinusitis Hevert SL; Sinusitis-Weliplex†; *Hung.*: Luffeel; Luffeel; *Neth.*: Bronchillte; Euphorbium comp; Holergie; Homeocare Allerio; Homeocare neusspray; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Lergilite; Luffanil; Luffeel H; Luffeel H; Nisyspray; Ricura; Sinufleur; *Rus.*: Aphlubin-Naze (Афлубин-Назе); Delufen (Делуфен); Rhinital (Ринитал); *S.Afr.*: Euphorbium Compositum S†; *Switz.*: A Vogel pour les sinus; A Vogel Spray contre le rhume des foins; HerbAllerg; Pollinosan†; *Ukr.*: Delufen (Делуфен); Rhinital (Ринитал).

Lungmoss

Lung Lichen; Lunglav; Lungwort; Oak Lungwort; Tree Lungwort.
UNII — D1YM0P5Z2T.

NOTE. The names lungmoss, lungwort, and oak lungs have also been applied to the plant *Pulmonaria officinalis*.

Profile

Lungmoss, the lichen *Lobaria pulmonaria* (*Sticta pulmonaria*) (Lobariaceae), is included in herbal medicines for pulmonary disorders.

Homoeopathy

Lungmoss has been used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Port.*: Stodal.

Homoeopathic Preparations. *Austral.*: Hay Fever; *Austria*: Anfokali; Bronchalis-Heel; *Canad.*: Allergies; Bronkeel†; Hay Fever; Homeo-Form AL†; Homeo-Form SI†; Kids Allergies; Nareel†; *Sinus*; *Cz.*: Bronchalis-Heel; Stodal; *Fr.*: Homeodose 8†; Stodal; Stodal; *Ger.*: Jutussin; Pulmo Bronchialcomplex; Pulmo Bronchialcomplex; Schleimhaut-Komplex I; Ho-Fu-Complex; *Hung.*: Anfokali; Bronchalis-Heel; Naso-Heel S; Stodal; *Neth.*: Bronchalis; Jutussin R9; Stodal; *Rus.*: Stodal (Стодаль); *Switz.*: Bronchalis-Heel; Regenaplex Nr. 24c; Stodal; *Ukr.*: Stodal (Стодаль); *USA*: Preferred Remedies Allergy; Preferred Remedies Sinus.

Luprostiol *(BAN, rINN)*

Luprostiol; Luprostiolum; Люпростиол.
(±)-(Z)-7-{(1*S*,2*R*,3*R*,5*S*)-2-[(2*S*)-3-(3-Chlorophenoxy)-2-hydroxypropylthio]-3,5-dihydroxycyclopentyl}hept-5-enoic acid.
$C_{23}H_{39}ClO_6S$=445.0
CAS — 67110-79-6.
ATC Vet — QG02AD91.
UNII — HWR60H5GZB.

Profile

Luprostiol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Lupulus

Apynių spurgai; Chmelová šištice; Hop Strobile; Hopfenzapfen; Hops; Houblon; Houblon, cône de; Humalankukka; Humlekotte; Humulus; Komlótoboz; Lúpuli flos; Lupuli Strobulus; Lúpulo; Strobili Lupuli; Szyszka chmielu.
ATC Herb — HN05CM5004 (Humulus lupulus: cone); HA09WA5015 (Humulus lupulus: cone); HN05CM5005 (Humulus lupulus: glandular hair).
UNII — 01G73H6H83.

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

Ph. Eur. 8: (Hop Strobile). The dried, generally whole, female inflorescences (strobiles) of the hop plant *Humulus lupulus*. It has a characteristic aromatic odour. Protect from light.

Profile

Lupulus has been used as a bitter, and supplies the characteristic flavour of beers. It is used in herbal and folk medicine as a sedative.

Homoeopathy

Lupulus has been used in homoeopathic medicines under the following names: Humulus lupulus; Lupulinum; Humulus lupulus e glandulis; Humulus; Lupul.

References.
1. Zanoli P, Zavatti M. Pharmacognostic and pharmacological profile of *Humulus lupulus* L. *J Ethnopharmacol* 2008; 116: 383–96.

Interactions. For a suggestion of a potential interaction between lupulus and tamoxifen, or other competitive oestrogen receptor antagonists, see Herbal Medicines, under Interactions of Tamoxifen, p. 863.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Novo-Passit (Ново-Пассит); *Swed.*: Valerina; *Switz.*: Klosterfrau Nervenruh Dragees.

Multi-ingredient Preparations. *Arg.*: Calmtabs; *Austral.*: Chill Pill; Cold & Flu Day/Night; Executive Sleep Formula; Extralife Sleep-Care†; Humulus Compound; Natural Deep Sleep†; Passionflower Plus†; PM Dreamtime; ReDormin; Sleep Easy; Tranquil Night; *Austria*: Baldracin; Hova; Montana; Nervenruh; Nerventee St Severin; Schlaf- und Beruhigungsdragees; Wechseltee St Severin; *Braz.*: Remilev; *Canad.*: Calm-Aid†; Detente†; Herbal Insomnia†; Herbal Nerve†; Myoplex†; Relax Plus; Relaxant; Relaxol; Salusan†; Sleep Relax; *Chile*: Cellenergy; Valupass; *Cz.*: Baldracin†; Calmonal†; Detsky Caj s Hermankem; Doppelherz Energie-Tonikum†; Fytokliman Planta; Hova; Novo-Passit; Sanason†; Species Nervinae Planta; Valofyt Neo†; *Fr.*: Diatisan†; Santane N; Tone; *Ger.*: Alluna Nacht†; Allunapret; Ardeysedon; Avedorm duo†; Baldrian-Dispert Nacht†; Einschlaf-Kapseln extra†; Granu Fink Femina; Ilja Rogoff; Kneipp Gute Nacht†; Kytta-Sedativum; Moradorm S; Nervenkapseln; Pascosedon; Sedacur; Sedaselect D; Selon; *Gr.*: Vivinox; *Hung.*: Cirkulin Valeriana; Doppelherz Energie Tonikum N; Hova; Kalms; Montana; ReDormin; Sedacur; *Irl.*: Avena Sativa Comp; Quiet Life; *Israel*: Nerven-Dragees; Redormin Night; *Ital.*: Altadrine Firming†; Calmason; Emmenoiasi; Eugune; Osteo Complex; *Jpn*: Eki Cabe A†; *Mex.*: Ivel†; Nervinetas; *Neth.*: Plantival; *Norw.*: Valerina Natt; *Philipp.*: Sleepasil; *Pol.*: Calmina; Doppelherz Energovital Tonik†; Hova; Kalms; Klimax; Lekosen†; Lumewal; Lunapret; Nervendragees; Nervinolum; Nervinum†; Nervomix; Nervosol; Nerwobonisol; Passispasmin; Passispasmol†; Sedomix; Somnoten†; Tabletki Uspokajajace; Vallup†; Valuherb; Valused; *Rus.*: Cedoflor (Седофлор); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Kliophyt (Клиофит); Passifit (Пассифит); Sanason (Санасон); Sedativae Species No 2 (Седативный Сбор 2); Urocholesan (Урохолесан); Urolesan (Уролесан); *S.Afr.*: Avena Sativa Comp†; *Spain*: Tranquigor; *Swed.*: Dormeasan; Sedacur; *Switz.*: Baldriparan; Dormeasan; Dragees pour la detente nerveuse et le sommeil†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Gouttes pour le coeur et les nerfs; Hova; Hyperiforce comp; Nervinetten; ReDormin; Relaxo; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Valverde Coeur; Valverde Sommeil; Zeller Sommeil; *UK*: Anased; Avena Sativa Comp; Chamomile Blend; Dormeasan; Estroven Nighttime; Gerard House Serenity; Gerard House Somnus; Goodnight; HRI Calm Life; HRI Night; Kalms Day; Kalms Sleep; Kalms; Natrasleep; Neurotone; Newrelax; Nodoff; Nytol Herbal; Puncto SleepTight; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B+; Slumber; Sominex Herbal; Stressless; Unwind Herbal Nytol; Valerian Passiflora and Hops; Valerina Night-Time; Ymea; *Ukr.*: Florised (Флорисед); Herbastress (Гербастресс); Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Lifemin (Лайфемин); Novo-Passit (Ново-Пассит); Sanason (Санасон)†; Sedavit (Седавит); Trivalumen (Тривалумен); Urochol (Урохол)†; Urolesan (Уролесан); *Venez.*: Insocaps; Lupassin; Nervinetas.

Homoeopathic Preparations. *Austral.*: Sleep & Insomnia Relief; *Austria*: Valerianaheel; *Canad.*: Calms Forte; Calsom†; Hylands Formula C; Hylands Formula CF; Valerianaheel Comp†; *Ger.*: Alho-Sedosan; Antimast TN†; Avena sativa comp†; Dormi-cyl L; Ho-Len-Complex; Dormi-Gastreu 5 R14; Nervoregin; Neuro-Ginsan N; Passiflora Complex†; Seda-Do; Sedacalman; Sedaphin†; Thyreo-Injektopas; Tondinel H; *Neth.*: Weleda Avena Valeriana; *Rus.*: Passidorm (Пассидорм); *Switz.*: Nelsons Nocturat†; *USA*: Preferred Remedies Sleep.

Lycopene

E160(d); Ликопин.
$C_{40}H_{56}$=536.9
CAS — 502-65-8 (all-trans lycopene).
UNII — SB0N2N0WV6.

Pharmacopoeias. In *US* which also includes Tomato Extract Containing Lycopene.

USP 36: (Lycopene). A mixture of geometrical isomers of lycopene. Store in airtight containers under an inert gas at a temperature of 8 degrees to 15 degrees. Protect from light.

Profile

Lycopene is a carotenoid responsible for the red colour of tomatoes and some other fruits including rose fruit (p. 2607.1). Many isomeric forms of lycopene are possible but the *all-trans* lycopene is the most common form present in food. Lycopene is used as a colouring agent and antoxidant. Much interest has been expressed in the antoxidant properties of lycopene for the potential prevention of diseases such as cardiovascular disease and some cancers, particularly of the prostate gland. Lycopene is used as a dietary supplement and is also an ingredient of some skin preparations; it has also been included in oral tanning preparations.

References.
1. Rao AV, *et al.* Lycopene. *Adv Food Nutr Res* 2006; 51: 99–164.
2. Riccioni G, *et al.* Protective effect of lycopene in cardiovascular disease. *Eur Rev Med Pharmacol Sci* 2008; 12: 183–90.

Malignant neoplasms. There has been continuing interest in the potential role of tomatoes and lycopene in the prevention of various cancers.[1,2] However, an evidence-based review of the literature by the FDA[3] concluded that there was no credible evidence to support claims that tomatoes or tomato-based foods reduced the risk for lung, colorectal, breast, cervical, or endometrial cancer. The FDA also concluded that there was very limited credible evidence for qualified health claims for tomatoes or tomato sauce and a reduced risk of prostate, gastric, ovarian, and pancreatic cancers. They also found no credible evidence to support health claims for lycopene and a reduced risk of any of the cancers evaluated.

1. Everson KM, McQueen CE. Lycopene for prevention and treatment of prostate cancer. *Am J Health-Syst Pharm* 2004; 61: 1562–6.
2. Dahan K, *et al.* Lycopene in the prevention of prostate cancer. *J Soc Integ Oncol* 2008; 6: 29–36.
3. Kavanaugh CJ, *et al.* The U.S. Food and Drug Administration's evidence based review for qualified health claims: tomatoes, lycopene, and cancer. *J Natl Cancer Inst* 2007; 99: 1074–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Licopenox; *Braz.*: Licco; *Chile*: Lycoprost; *India*: Lycbound; Lycorich Plus; *UK*: Atero non.

Multi-ingredient Preparations. *Arg.*: Natubrown; Prostamen Reversal; Selder; *Austral.*: Advanced Prostate Care; Homme-F Menevit; Prostate Care; Womens Multi; *Braz.*: Licopene† Licovit; Licoxid; Lymium; Tomat; *Chile*: Dennov; *Fr.*: Acty mine†; Actypral†; Anti-oxydant 200; Anti-oxydant F4; Corvi tec; GliSODine Solaire; Imedeen Prime Renewal†; Imedeen Tar Optimizer†; Oxelio Topique; Phytosolaire†; *Hong Kong*: Pal metto Plus†; *India*: Actioner; Adrovit; Alcored; Aritom-L; Asi Min MV; Aza Cap; Basix-LB; Betagan Forte; Betonin-XT; C Rich; Cad-11; Cadred; Calorex; Calorex; Cardistim; Coq Forte Crotec-BC; Diasafe; Doravit Forte; Ecome-LY; Elgrape; Elnutra M; Elnutra; Enduranz; Evion Forte; Exerge; Feribest-L; Fol-G2 Furtipil-L; Gardian; Gatdor; Gemvit; GV-24; Hi-Q; Hyrase Immunace Forte; Imuvit; Ipene; Joyce; Keeper Plus; L-Bex; L Mato; L-Nit; L-Vit-Z; Layo; Leclub; Legain; Lifored; Lizace Lutamin; Lutivit; Lyco-First; Lyco-First; Lycoact; Lycoage; Lyco bal Forte; Lycobel; Lycobel; Lycobig; Lycobion; Lycobond Lycocare; Lycocos; Lycoden-M; Lycodric; Lycofact Plus; Lycofit Lycofol; Lycofresh; Lycogold; Lycogreen; Lycolar; Lycolife Lycomato; Lycomato; Lycomax; Lycomin; Lycomint; Lycomin vit; Lyconerve; Lyconet Green; Lyconia; Lyconova; Lycoral-2 Lycored; Lycos-CZ; Lycosel; Lycoshine; Lycosim; Lycosta Lycosta; Lycostar-CM; Lycostar; Lycoswift; Lycosym; Lycosyn Lycour; Lycovit; Lycoxy; Lycozin; Lycra; Lynet; Lyrich-G; Lyr ich; Lyrich; Lyto; Lytox; Megagin; Memi-LB; Mitavin; Momvi ta; Multilipius; Multivite Gold; Multivite Vision; Multivit Woman; Multoxid; Myco-L; N-Rich; Natoz; NBOxid; Nervi Plus; Neuroage Plus; Neuroage Plus; Niloxid; Nislutin; Nutiva Lyco; Olyco Plus; Omaato; Oncovit; Orymax; Orymax; Oxyla AL; Oxylyco; *Indon.*: Amaropo Plus; Antox; Kapset; Legre Legreskin; Liproqy; Lycoq†; Lycoten; Lycoxy; Lyphen; Noro Ocu-V; Optha-LL; Optimax Plus; Optimax; Oxypen; Reticoper Retivit Plus; Stacare; *Israel*: Multivitamin; Quantum; *Ital* Adrusen; Zeadema Crono; *Malaysia*: Glow; Lycovid; Pynocare white; *Philipp.*: Gloww; Havitall; Nutricap; Nutrotal; Polyner E with lecithin; *Singapore*: Glow; Palmetto Plus†; Vitaton Gold *Turk.*: Prostamen; *Ukr.*: Oko-Health (Око-хелс); OxyLi (ОксиЛит); *USA*: Alive Mens Energy; Bladder 2.2; Cardio Ton Certavite Senior with Antioxidant Nutrients; Clinical Nutrien 50-Plus Men; Corvita; Corvite Free; Fitness Tabs for Men; Fi ness Tabs for Women; Immunicare; Ocuvite Eye + Multi; On A Day Men's Health Formula; PreQue 10; REQ49+; Triveer Ten; Udamin SP; Udamin.

Lycopodium

Blitzpulver; Hexenmehl; Licopodio; Lycopod; Lycopode Streupulver; Vegetable Sulfur; Vegetable Sulphur; Witch Meal.
CAS — 8023-70-9.
ATC Herb — HD02WX5003 (Lycopodium clavatum: spore).
UNII — C88X29Y479.

Profile

Lycopodium, the spores of *Lycopodium clavatum* (see p. 2547.1) and related species, has been used as a pharmaceutical excipient and in herbal medicines for liver and biliary-tract disorders. It was also formerly used for bladder disorders and in dusting powder for skin conditions.

Lycopodium is flammable and has been included in explosives and fireworks.

Homoeopathy

Lycopodium has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Magnesia Phosphorica I Oligoplex.

Homoeopathic Preparations. *Austral.*: Homoderma; IBS Eze; Stomach Calm; *Canad.*: Bioactiv R†; Bioactiv S†; Calms Forte 4 Kids; Comp-Drops 8 Uri-Tract†; Cynara Complex†; Earache; Formula ES 211; Formula FV 213; Indigestion†; *Chile*: Arnica Hamamelis Compuesta; Bioactiv R; Bioactiv S; Silik; *Fr.*: Abbe Chaupitre no 59†; Abbe Chaupitre no 79†; Amphosca Orchitine; Amphosca Ovarine; Basilicum Complexe No 96; Boripharm No 15†; Grindelia Complexe No 58; Homeodose 24†; L 114; Myosotis Complexe No 63†; Natrum Carbonicum Complexe No 10†; Yucca Complexe No 110; *Ger.*: Bomagall; Cholo 2-injektopas; Galloselect; Haemorrhoid-Gastreu N; Hepa-Gastreu N R7; Hepa-Loges N; Hepar comp; Hevertnier Complex N†; Hexacyl; Juv 110; Leber Albin; Lymphdiaral; Pancreas-Gastreu N; Stoma-Gastreu S R5; Tondinel.

Lycopodium Clavatum

Alimindelig Ulvefod; Barlapp; Buck Horn; Clavatum; Club Moss; Common Clubmoss; Elk-moss; Foxtail; Ground Pine; Katinlieko; Keulenbärlapp; Mattlummer; Metsäkatinlieko; Plavuň Obyčajný; Plavuň Vidlačka; Running Clubmoss; Shen Jin Cao; Stag's-horn Clubmoss; Vanlig Mattlummer; Wolf's Claw.

ATC Herb — HG04BW5021 (Lycopodium clavatum herb).

UNII — 005ICF6L27.

Profile

The aerial parts of *Lycopodium clavatum* (Lycopodiaceae) have traditionally been used in herbal medicine for bladder and kidney disorders. Several species of *Lycopodium* are reported to contain toxic alkaloids. The spores of *Lycopodium clavatum*, known as Lycopodium, are also used (see p. 2546.3).

Homoeopathy

Lycopodium clavatum has been used in homoeopathic medicine.

References.

1. Ma X, Gang DR. The Lycopodium alkaloids. *Nat Prod Rep* 2004; 21: 752–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Toxicol; *Malaysia*: Elgucare.

Homoeopathic Preparations. *Austral.*: Respatona Nasal Spray Decongestant; *Austria*: Lymphdiaral; Nux Vomica-Homaccord; *Canad.*: Adrisin†; Amphosca†; Carduus Plex†; Cruroheel S†; Digestion; Headache & Migraine; Hecocur†; Hepar Compositum; Homeo-Form MI†; Homeo-Form PMT†; Hylands Gas; Jet Lag; PMS; Rhinar†; *Chile*: Artroplex; Bioactiv P; Bioactiv I; *Cz.*: Hepeel; *Fr.*: Cimicifuga Complexe No 21†; *Ger.*: Asthmakhell N; Choanol N; Colintest-Gastreu; Heparanox H; Lowe-Komplex Nr 6; Marianon Hepar; Nuxal comp; Nuxal H; Ventrigutt M; *Hung.*: Hepeel; *Neth.*: Acidolite; Aesculus Comp; Ambheel; Apo-Hepat; Asakell; Asthmakhell†; Bronchilite; Colintest-Gastreu R37; Dermafleur; Dermalite; Dolilite; Emvita 26; Emvita 7; Hemorrolite; Hepa-Gastreu R7; Hepalite; Hepeel H; Lymphdiaral; Nux Vomica-Homaccord; *Rus.*: Iris-Plus (Ирис-Плюс); Rhus-Plus (Рус-Плюс); *Switz.*: Hepeel; Regenaplex Nr. 31b; Regenaplex Nr. 51c; *Ukr.*: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); *USA*: Preferred Remedies Stress.

Lysergide *(BAN, rINN)*

Lisergida; Lisérgido; LSD; LSD-25; Lysergic Acid Diethylamide; Lysergidum; Лизергид.

(+)-*NN*-Diethyl-D-lysergamide; (6a*R*,9*R*)-*NN*-Diethyl-4,6,6a,7,8,9-hexahydro-7-methylindolo[4,3-*fg*]quinoline-9-carboxamide.

$C_{20}H_{25}N_3O$=323.4.

CAS — 50-37-3.

UNII — 8MA5SWF92O (lysergide); 5S94F6A36E (l-lysergide).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of lysergide:

25; 25s; 100s; A; Acid; Acid tabs; Acido; Aeon flux; Alice; Alphabet; Angel tears; Angry paper; Animal; Barrels; Bart Simpson; Battery acid; Beast; Beavis & Butthead; Bells; Bevis & Butthead; Big D; Big daddy; Bird head; Birdhead; Black acid; Black star; Black sunshine; Black tabs; Blackbird; Blaze; Blotter; Blotter acid; Blotter cube; Blotters; Blue acid; Blue barrels; Blue chairs; Blue cheers; Blue fly; Blue heaven; Blue heavens; Blue microdot; Blue mist; Blue moons; Blue star; Blue tabs; Blue vials; Boomers; Brown bombers; Brown dots; Buvard; California sunshine; Cap; Caps; Casper the ghost; Caviar; Cheap basing; Cheers; Chief; Chinese dragons; Cid-drip the entertainer; Chocolate chips; Church; Cid; Class; Coffee; Colors; Comic book; Conductor; Contact lens; Crackers; Crystal; Crystal tea; Cube; Cupcakes; D; Deeda; Dental floss; Diablo; Dinosaurs; Domes; Dose; Doses; Dosure; Dots; Double dome; Dragon; DSL; El Cid; Electric Kool Aid; Ellis Day; Elvis; Eye Candy; Felix; Felix the Cat; Fields; Flash; Flashers; Flat blues; Flats; Flying triangle; Frogs; Fry; Gel; Gel caps; Gelatine squares; Geltab; Ghost; God's flesh; Golden dragon; Golf balls; Goofy's; Gooney birds; Grape parfait; Green double domes; Green single dome; Green single domes; Green wedge; Grey shields; Groovy lemon; Hats; Hawaiian sunshine; Hawk; Haze; Head light; Head lights; Headlights; Heaven; Heavenly; Heavenly blue; Illusions; Infinity; Instant zen; Jesus Christ acid; Kaliedescope; Keys to the kingdom; L; LAD; Lake Shore Drive; Laogor; Lason daga; Lason sa daga; Lavender; LBJ; Leary's; Lenos; Lens; Lids; Lime acid; Little smoke; Live, Spit and Die; Logor; Loony Toons; LSD; LSD-25; Lucy; Lucy in the sky with diamonds; Magic Tickets; Mellow yellow; Mickey's; Microdot; Microdots; Midnight Quinn; Mighty Quinn; Mikes; Mind blow; Mind detergent; Mist; Mister Natural; Monstre rouge; Monstre vert; Monterey Purple; Moons; Mother of God; Newspapers; One way; One-way; Optical illusions; Orange ba; Orange barrels; Orange cubes; Orange haze; Orange micro; Orange sunshine; Orange wedges; Owsley; Owsley's acid; Owsley's blue dot; Ozzie's stuff; Pane; Paper; Paper acid; Peace; Peace tablets; Peaks; Pearly gates; Pellets; Pepa; Phoenix; Pills; Pink blotters; Pink panther; Pink robots; Pink wedge; Pink wedges; Pink witche; Pink witches; Pizza; Potato; Pure love; Purple barrels; Purple dome; Purple dots; Purple flats; Purple gel tabs; Purple haze; Purple hearts; Purple mikes; Purple ozoline; Purple wedge; Pyramid; Pyramids; Rain Drops; Rainbow; Recycle; Red lips; Rips; Royal blue; Royal blues; Roz-rox; Russian sickles; Sacrament; Sandoz; Serenity; Sheets; Shields; Sherman; Sid; Smears; Smiley; Snowmen; South parks; Specks; Square dancing tickets; Squirrel; Stamp; Stanley's stuff; Star; Strawberries; Strawberry; Strawberry fields; Sugar; Sugar cubes; Sugar lumps; Sunrise; Sunshine; Sunshine Acid; Superman; Syd; T; Tab; Tabs; Tail lights; Teddy bears; The Ghost; The Hawk; Ticket; Tickets; Ticket to ride; Timothy Leary; Timothy Leary Ticket; Trip; Trippers; Trips; Twenty-five; Uncle Sid; Uncle Sidney; Valley dolls; Vodka acid; Volcano 5; Vulcoes; Wafer; Waffles; Watercolors; Wedding bells; Wedge; Wedges; White dust; White lightning; White Owsley's; Window glass; Window pane; Woodstock; Yellow; Yellow dimples; Yellow sunshine; Yellows; Ying Yang; Zen; Zig Zag man.

Profile

Lysergide was formerly used therapeutically but is now encountered as a drug of abuse for its hallucinogenic and psychedelic properties.

There is considerable variation in individual reaction to lysergide. Disorders of visual perception are among the first and most constant reactions to lysergide. Subjects may be hypersensitive to sound. Extreme alterations of mood, depression, distortion of body image, depersonalisation, disorders of thought and time sense, and synaesthesia may be experienced. Anxiety, often amounting to panic, may occur (a 'bad trip'). Duration of effects may last for up to 12 hours after ingestion, although hallucinations can sometimes last up to 48 hours and psychoses for up to 4 days. The effects of lysergide may recur months after ingestion of lysergide; the recurrence or 'flashback' may be spontaneous or induced by alcohol, other drugs, stress, or fatigue.

The subjective effects of lysergide may be preceded or accompanied by somatic effects that are mainly sympathomimetic in nature and include mydriasis, tremor, hyperreflexia, hyperthermia, piloerection, muscle weakness, and ataxia. There may be nausea and vomiting and increased heart rate and blood pressure. Derangement of blood clotting mechanisms has been described. In addition, respiratory arrest, convulsions, and coma may result from overdoses. There is no evidence of fatal reactions to lysergide in man, although accidental deaths, suicides, and homicides have occurred during lysergide intoxication.

Tolerance develops to the behavioural effects of lysergide after several days and may be lost over a similar period. There is cross-tolerance between lysergide, mescaline, and psilocybine and psilocin, but not to amfetamine or to cannabis.

Physical dependence on lysergide does not seem to occur.

Mace Oil

Macis, aceite de; Мацисовое Масло.

ATC Herb — HM02AW5010 (Myristica fragrans essential oil); HA03AW5040 (Myristica fragrans essential oil).

UNII — 9KXX6I0U7Z.

NOTE. Mace has also been used as a name for solutions of chloroacetophenone (p. 2475.3), a tear gas.

Profile

Mace oil is a volatile oil obtained by distillation from mace, the arillus of the seed of *Myristica fragrans* (Myristicaceae).

Nutmeg (p. 2573.1) is the dried kernel of the seed of *M. fragrans*.

Mace is used as a flavour and carminative similarly to nutmeg. It has also been used with herbal substances and other volatile agents in preparations for musculoskeletal and respiratory-tract disorders. As with nutmeg, large doses of mace may cause epileptiform convulsions and hallucinations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: China-Eisenwein†; *Cz.*: Dr Theiss Schwedenbitter†; Original Schwedenbitter; *Hung.*: Bano Svedkeseru; *Rus.*: Himcolin (Химколин).

Macrogols

Macrogola; Macrogole; Macrogoles; Macrogoller; Makrogoler; Makrogoliai; Makrogolit; Makrogolok; Makrogoly; PEGs; Polietilen Glikoller; Polietilenglicoles; Polyethylene Glycols; Polyoxyethylene Glycols; Макроголы.

$CH_2(OH)(CH_2OCH_2)_mCH_2OH$. Alternatively some authorities use the general formula $H(OCH_2CH_2)_nOH$ when the number assigned to *n* for a specified macrogol is 1 more than that of *m* in the first formula.

CAS — 25322-68-3 (macrogols); 37361-15-2 (macrogol 300).

ATC — A06AD15.

ATC Vet — QA06AD15.

Nomenclature. Macrogol is *BAN* and *rINN*. The name is followed by a figure which corresponds approximately to its average molecular weight.

Pharmacopoeias. Macrogols of various molecular weights are included in many pharmacopoeias.

Eur. (see p. vii) has a general monograph describing macrogol 300, 400, 600, 1000, 1500, 3000, 3350, 4000, 6000, 8000, 20 000, and 35 000. *USNF* has a general monograph describing Polyethylene Glycol which requires that it be labelled with the average nominal molecular weight as part of the official title.

Ph. Eur. 8: (Macrogols). Mixtures of polymers with the general formula $H(OCH_2CH_2)_nOH$, where *n* represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

Macrogol 300, 400, and 600 are clear, viscous, colourless or almost colourless, hygroscopic liquids. Miscible with water; very soluble in alcohol, in acetone, and in dichloromethane.

Macrogol 1000 is a white or almost white, hygroscopic solid with a waxy or paraffin-like appearance. Very soluble in water; freely soluble in alcohol and in dichloromethane.

Macrogol 1500 is a white or almost white solid with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; freely soluble in alcohol.

Macrogol 3000 and 3350 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; very slightly soluble in alcohol.

Macrogol 4000, 6000, and 8000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water and in dichloromethane; practically insoluble in alcohol.

Macrogol 20 000 and 35 000 are white or almost white solids with a waxy or paraffin-like appearance. Very soluble in water; practically insoluble in alcohol; soluble in dichloromethane.

All macrogols are practically insoluble in fatty oils and in mineral oils. All macrogols should be stored in airtight containers.

USNF 31: (Polyethylene Glycol). Addition polymers of ethylene oxide and water, represented by the formula $H(OCH_2CH_2)_nOH$, in which *n* represents the average number of oxyethylene groups. They may contain a suitable antoxidant. Each macrogol is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight

increases, the water solubility, hygroscopicity, and solubility in organic solvents decrease, while the viscosity increases.

Liquid grades occur as clear to slightly hazy, colourless or practically colourless, slightly hygroscopic, viscous liquids, having a slight, characteristic odour. Solid grades occur as practically odourless, white, waxy, plastic material having 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 ethoxyethanol, in ethyl acetate, and in toluene; all grades are insoluble in ether and in hexane. The pH of a 5% solution of a macrogol in water is between 4.5 and 7.5.

Store in airtight containers.

Incompatibility. Macrogols can have oxidising activity leading to incompatibilities. The activity of bacitracin or benzylpenicillin may be reduced in a macrogol base. Some plastics are softened by macrogols.

Uses and Administration

Macrogols are relatively stable, non-toxic compounds which have a range of properties depending on their molecular weight. They are widely used in pharmaceutical manufacturing as water-soluble bases for topical preparations and suppositories, as solvents and vehicles, and as solubilising agents, tablet binders, plasticisers in film coating, and tablet lubricants. Macrogols of high molecular weight such as macrogol 4000 have been used as inert markers in studies on intestinal absorption and excretion.

A mixture of macrogol 3350 or 4000 with electrolytes is used for **bowel preparation** before colonoscopy, radiological procedures, or surgery. These preparations have been formulated so that the osmotic activity of the macrogol and concentrations of the electrolytes result in a minimum net effect on the fluid and electrolyte balance. Reconstituted aqueous solutions of different preparations contain about 59 g, 60 g, 100 g, or 105 g of the macrogol per litre. The method of administration is similar for most preparations irrespective of the concentration of macrogol in the final solution. Adults are given 200 to 300 mL of the reconstituted aqueous solution, which should be swallowed rapidly, and this is repeated every 10 to 15 minutes until the rectal effluent is clear, or until a total of 3 to 4 litres of the solution has been consumed. Alternatively, 2 litres of reconstituted solution is taken in the evening preceding the clinical procedure, and a further 2 litres early in the morning on the day of the procedure. Bowel evacuation usually begins about 1 hour after starting dosage and is complete in about 4 hours. Patients should take no solid food for at least 2 hours before starting the course, although best results are obtained if the period of fasting is 3 to 4 hours. The manufacturer of one preparation containing 100 g of macrogol 3350 per litre recommends a different regimen of just 2 litres of reconstituted solution for the whole course: one litre is drunk over a period of 1 to 2 hours followed by a further litre after 1.5 hours on the evening before the procedure; alternatively, the course can be split into one litre on the evening before and one litre on the morning of the procedure so that the course finishes at least one hour before the procedure. An additional one litre of clear fluid should also be consumed during the course and no solid food should be taken from the start of the course until after the clinical procedure. Some manufacturers recommend that the reconstituted solution is more palatable if chilled, although chilled solutions are not recommended for infants. There has also been a report of hypothermia developing in a patient after consuming a large volume of the chilled solution. Additional flavouring ingredients, sugar, or other sweeteners should not be added to the solution. If distension or pain occur, dosage should be temporarily stopped or the interval between drinks extended. Some preparations may also be given by nasogastric tube at a rate of 20 to 30 mL/min.

A solution containing 105 g of macrogol 3350 per litre is used for the treatment of **chronic constipation** in a usual oral dose of 125 mL up to three times daily. For some preparations, the solution is made up to a lower volume of 62.5 mL although the final concentration of macrogol 3350 remains at 105 g per litre. The maximum course is 2 weeks, which may be repeated if necessary; extended use may be required in some circumstances in which case a reduction in dose could be considered.

A solution containing 105 g of macrogol 3350 per litre is used in the management of **faecal impaction**; one litre of this solution should be consumed within 6 hours each day for a maximum of 3 days. Patients with impaired cardiovascular function should take no more than 250 mL in any one hour.

For doses of macrogol preparations in children, see Administration in Children below.

Conjugation of drugs and therapeutic proteins with macrogols (**pegylation**) has been tried in an attempt to improve their pharmacokinetic profiles and to reduce their adverse effects. Pegylation may also reduce the immunogenicity of therapeutic proteins. Examples of pegylated proteins include pegademase (p. 2584.3), pegaspargase (p. 743.3), and peginterferon alfa (see Uses and Administration of Interferon Alfa, p. 989.2).

Administration in children. Solutions of macrogols with electrolytes are used for **bowel preparation** in children in varying dosage regimens. A solution containing 105 g of macrogol 3350 per litre may be given orally or by nasogastric tube to children aged over 6 months in a dose of 25 mL/kg per hour until the rectal effluent is clear; children under 2 years of age should be monitored for hypoglycaemia since these solutions contain no caloric substrate. A solution containing 59 g of macrogol 4000 per litre may be given to children aged over 5 years and weighing over 20 kg in an oral dose of one litre of solution per 15 to 20 kg. For general details on administration of macrogol solutions, see under Uses and Administration above.

A solution containing 105 g of macrogol 3350 per litre is given orally to children with **chronic constipation**. The usual initial daily dose for those aged 2 to 6 years is 62.5 mL, and for those aged 7 to 11 years, 125 mL. Thereafter, the dose should be increased or decreased as necessary to produce regular soft stools; the usual maximum dose is 250 mL daily. Treatment for prolonged periods may be required in children, although safety and efficacy have only been proved for up to 3 months of treatment. It is recommended that treatment is stopped gradually and resumed if constipation occurs. The *BNFC* also recommends a dose of 31.25 to 62.5 mL daily in children under 1 year for the treatment of chronic constipation.

A solution containing 105 g of macrogol 3350 per litre is given orally to children aged 5 to 11 years for **faecal impaction** in an escalating dose until disimpaction occurs up to a maximum of 7 days. Four doses of 62.5 mL of solution are given initially on the first day, increasing by 2 doses daily to a maximum of 12 doses daily on days 5 to 7; the total daily dose should be divided and consumed within a 12-hour period. Doses for prevention of recurrence of faecal impaction in children are as for children's doses for chronic constipation (see above). The *BNFC* recommends that children aged 1 to 5 years with faecal impaction may be given two doses of 62.5 mL of solution on the first day, then four doses daily for 2 days, then 6 doses daily for 2 days, and finally 8 doses daily until impaction resolves. It also recommends a dose of 31.25 to 62.5 mL daily in children under 1 year.

Doses of macrogols for the treatment of chronic constipation and faecal impaction for those aged 12 years and over are given under Uses and Administration above.

Drug delivery systems. References to the use of macrogols in delivery systems for drugs and proteins.

1. Reddy KR. Controlled-release, pegylation, liposomal formulations: new mechanisms in the delivery of injectable drugs. *Ann Pharmacother* 2000; 34: 915–23.
2. Harris JM, *et al.* Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet* 2001; 40: 539–51.

Phenol poisoning. Washing with liquid macrogols has been recommended in the emergency treatment of skin contamination with phenol, see p. 1764.3.

Adverse Effects and Precautions

Macrogols appear to have relatively low toxicity, although any toxicity appears to be greatest with the macrogols of low molecular weight. They may cause stinging when used topically, especially on mucous membranes, and have been associated with hypersensitivity reactions such as urticaria. Hyperosmolality, metabolic acidosis, and renal failure have been reported after topical application of macrogols to burn patients. Topical preparations with a macrogol base should therefore be used with caution in patients with renal impairment and/or large areas of raw surfaces, burns, or open wounds.

Patients undergoing bowel cleansing with mixtures of macrogols (3350 or 4000) and electrolytes commonly have local gastrointestinal discomfort, bloating, and nausea. Abdominal cramps, vomiting, and anal irritation may also occur and there have been rare reports of possible hypersensitivity reactions. These colonic lavage solutions are contra-indicated in gastrointestinal obstruction or perforation, ileus, gastric retention, peptic ulcer disease, and toxic megacolon; caution is advisable in patients with ulcerative colitis. Since aspiration may be a problem, they should be used with caution in patients with an impaired gag reflex, reflux oesophagitis, or diminished levels of consciousness. They should be given with caution to diabetic patients. Drugs taken within one hour of starting colonic lavage with an oral macrogol and electrolyte mixture may be flushed from the gastrointestinal tract unabsorbed.

Effects on fluid and electrolyte homoeostasis. A syndrome of elevated total serum calcium (with a concomitant decrease in ionised calcium), hyperosmolality, metabolic acidosis, and renal failure has been seen in *animals*[1] and in burn patients[2] after the topical application of preparations with a macrogol base. The *FDA* has recommended that topical preparations containing macrogol should be used with caution in burn patients with known or suspected renal impairment, as macrogols absorbed through denuded skin and not excreted normally by a compromised kidney could lead to symptoms of progressive renal impairment.[3]

The use of macrogol and electrolyte solutions for bowel preparation has also been associated with sodium and water retention, resulting in exacerbation of heart failure in a patient with diabetic gastroparesis,[4] and with the development of pulmonary oedema possibly due to aspiration in a child without cardiac or renal disease.[5]

1. Herold DA, *et al.* Toxicity of topical polyethylene glycol. *Toxicol App Pharmacol* 1982; 65: 329–35.
2. Bruns DE, *et al.* Polyethylene glycol intoxication in burn patients. *Burn* 1982; 9: 49–52.
3. Anonymous. Topical PEG in burn ointments. *FDA Drug Bull* 1982; 12: 25–6.
4. Granberry MC, *et al.* Exacerbation of congestive heart failure after administration of polyethylene glycol-electrolyte lavage solution. *Ann Pharmacother* 1995; 29: 1232–5.
5. Paap CM, Ehrlich R. Acute pulmonary edema after polyethylene glycol intestinal lavage in a child. *Ann Pharmacother* 1993; 27: 1044–7.

Hypersensitivity. Hypersensitivity to macrogols is uncommon but both immediate urticarial reactions and delayed allergic contact dermatitis have been reported after the topical application of preparations with a macrogol vehicle or base.[1] An anaphylactic reaction has been associated with the ingestion of macrogols in a multivitamin tablet.[2] The manufacturers of preparations containing macrogols and electrolytes for bowel cleansing have reported isolated instances of skin reactions and rhinorrhoea.

1. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978; 4: 135–8.
2. Kwee YN, Dolovich J. Anaphylaxis to polyethylene glycol (PEG) in a multivitamin tablet. *J Allergy Clin Immunol* 1982; 69: 138.

Overdosage. Ingestion of 2 litres of a colonic lavage solution containing macrogol 400 instead of macrogol 4000 resulted in a patient developing severe metabolic acidosis due to systemic absorption of the macrogol. The patient rapidly became comatose but was successfully treated with intravenous bicarbonate and dialysis.[1]

1. Bélaïche J, *et al.* Coma acidosique après préparation colique par du polyéthylène glycol. *Gastroenterol Clin Biol* 1983; 7: 426–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies macrogols as not porphyrinogenic; they 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)

Toxicity. For reports of macrogol (polyethylene glycol) 400 toxicity when included in some preparations of benzodiazepines, see under Propylene Glycol, p. 2205.3.

Pharmacokinetics

Liquid macrogols may be absorbed when taken orally but macrogols of high molecular weight, such as macrogol 3350, are not significantly absorbed from the gastrointestinal tract. There is evidence of absorption of macrogols when applied to damaged skin. Macrogols entering the systemic circulation are mainly excreted unchanged in the urine; low-molecular-weight macrogols may be partly metabolised.

References.

1. DiPiro JT, *et al.* Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. *Clin Pharm* 1986; 5: 153–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Osmolagrimas; *Austral.*: OsmoLax; *Austria*: DrinkaLax†; Forlax; MixaLax†; *Belg.*: Forlax; *Braz.*: Harmolax; *Canad.*: Lax-a-Day; Pegalax; Relaxa; Restoralax; Sealax†; *China*: Chang Song (长松); Forlax (福松); Run Ke Long (润可隆); You Sai Le (优赛乐); *Cz.*: Forlax; Oripeg; *Denm.*: Nuvolax; *Fin.*: Pegorion; *Fr.*: Biopeg; Forlax; *Ger.*: Bellymed; Dulcolax M Balance; Glandomed; Laxofalk; *Gr.*: Tanilas; Transorbin; *Hong Kong*: Forlax; *Hung.*: Forlax; *India*: Ezlax; Laxopeg; *Irl.*: Idrolax; *Israel*: Moviprep; Normalax; Peglax; *Ital.*: Kronys; Onilpeg; Paxabel; Pergidal; *Malaysia*: Blink Intensive Tears; Forlax; *Mex.*: Contumax; *Neth.*: Forlax; *Pol.*: Forlax; Olopeg; Prolaxatan†; *Port.*: Forlax; Philenterol†; Transipeg†; *Rus.*: Forlax (Форлакс); Osmogol (Осмогол); Polyoxidin (Полиоксидин); Realaxan (Реалаксан); *Singapore*: Blink Intensive Tears; Forlax; *Spain*: Casenlax; Micralax Macrogol; *Swed.*: Forlax; *Thai.*: Forlax; *Turk.*: Transipeg†; *UK*: Dulcobalance; PegLax; *Ukr.*: Diagnol (Диагнол); Forlax (Форлакс); *USA*: Dulcolax Balance; GaviLAX; GlycoLax; MiraLax.

Multi-ingredient Preparations. *Arg.*: Adital; Barex; Irix Lagrimas; Systane; Tractoclin; Transipeg; Visine Lagrimas; Visine Plus; *Austral.*: Colonlytely; Colonprep; Glycoprep-C; Glycoprep; Movicol; Prep Kit-C; Systane; Visine Advanced Relief; *Austria*: Endofalk; Klean-Prep; Molaxole; Movicol; Moviprep; *Belg.*: Colofort; Colopeg; Delpeg†; Endofalk; Endopeg; Klean-Prep; Laxido; Molaxole; Movicol; Moviprep; Precosol; Transipeg; *Braz.*: Mirugell; Muvinlax; NuLytely; *Canad.*: Bi-PegLyte; CoLyte; GoLytely; Klean-Prep; Lubricating Nasal Gel; Lubricating Nasal Mist; Moviprep; Peglyte; Rhinaris; Salinex Nasal Lubricant; Secaris; Systane; Visine Advance Triple Action; Visine Cool; *Chile*: Endofalk; Systane; Tears Visine†; *China*: Fortrans (福静清); Movicol (默维可); ShuTaiQing (舒泰清); Systane (思然); ZhengQing (正清); *Cz.*: Fortrans; Maxellax; Molaxole; Movicol†; Moviprep; *Denm.*: Encol; Endofalk; Gangiden; Lacrofarm; Magenterol; Movicol; Moviprep; Moxalole; *Fin.*: Colonsoft; Colonsteril; Endofalk; Klean-Prep†; Lacrofarm; Laxido; Laxiriva; Movicol; Moviprep; Moxalole; Olopeg; *Fr.*: Colopeg; Fortrans; Klean-Prep; Movicol; Moviprep; Moxalole; SST†; Systane; Transipeg; *Ger.*: Darmspulpulver; Darmspulung†; Delcoprep; Endofalk; Isomol; Klean-Prep; Laxatan M; Lefax Activolax; Macrogol; Movicol; Moviprep; Oralav; *Gr.*: Endofalk; Fortrans; GoLytely; Izetafin; Klean-Prep; Movicol; *Hong Kong*: Clinac OC; Fortrans; Hypotears; Klean-Prep; Movicol†; Systane; Visine Moisturizing†; *India*: Colocleen; Colopeg; Endopeg; *Indon.*: Laxarec; Microlax; Niflec; Systane; Visine Extra; *Irl.*: Klean-Prep; Laxido; Molaxole; Movicol; Moviliel; Moviprep; Movitev; Transipeg†; *Israel*: Meroken New; Systan UL; Systane; *Ital.*: Hypotears; Isocolan; Klean-Prep; Macro-P; Molaxole; Movicol; Moviprep; Selg-Esse; Selg; Systane; *Malaysia*: Fortrans; Hypotears; Systane; *Mex.*: NuLytely; Systane; Visine Extra; *Neth.*: Colofort; Eleprep†; Endofalk; Klean-Prep; Laxtra; Molaxole; Movicolon; Moviprep; Transipeg; *Norw.*: Endofalk; Laxabon; Movicol; Moviprep; Moxalole; *NZ*: Klean-Prep; Movicol; Moviprep; Prepkit-C; Visine Advanced Relief; *Philipp.*: Moisturizing All Clear; Systane; Visine Refresh; *Pol.*: Fortrans; *Port.*: Endofalk; Fortrans; Klean-Prep; Movicol; Pecol; *Rus.*: Endofalk (Эндофальк); Fortrans (Фортранс); Lavacole (Лавакол); Transipeg (Транзипег); *S.Afr.*: GoLytely; Klean-Prep; Movicol; Pegicol; *Singapore*: Fortrans; Klean-Prep; Movicol; Peglyte; Systane; *Spain*: Casenglicol; Evacuante Simple; Klean-Prep; Molaxole; Movicol; Moviprep; Solucion Evacuante; *Swed.*: Endofalk; Lacrofarm; Laxabon; Laxido; Laxiriva; Movicol; Movprep; Moxalole; Omnicol; Omnilax; *Switz.*: Colo-Sol; Cololyt; Fordtran†; Hypotears; Isocolan; Klean-Prep; Molaxole; Movicol; Moviprep; Nose Fresh; Pegicol; Transipeg; *Thai.*: Niflec; Systane; *Turk.*: Endofalk; GoLytely; Movicol; Systane; *UK*: Artelac Rebalance; Blink Intensive Tears; Klean-Prep; Laxido; Molaxole; Movicol; Moviprep; SST; Zerozole†; *Ukr.*: Endofalk (Эндофальк); Fortrans (Фортранс); *USA*: Advanced Relief Visine; Blink Gel Tears; CoLyte; GaviLyte; GoLytely; HalfLytely and Bisacodyl Bowel Prep Kit; Hypotears; MoviPrep; Nu-Tears II; NuLytely; OCL; Suclear; Systane; TriLyte; Visine Maximum Redness Relief; Visine Pure Tears; Visine Tears; Visine Tired Eye Relief; Visine Totality Multi-Symptom Relief; *Venez.*: Systane.

Pharmacopoeial Preparations
USP 36: PEG 3350 and Electrolytes for Oral Solution.

Magnesium Glutamate Hydrobromide

Bromoglutamato magnésico; Glutamato magnésico, hidrobromuro de; Hidrobromuro de alfa-aminoglutamato magnésico; Magnesium α-Aminoglutarate Hydrobromide; Magnesium Bromoglutamate.
$(C_5H_8NO_4)_2Mg.HBr=397.5$
CAS — 53459-38-4.

Profile

Magnesium glutamate hydrobromide has been used as a sedative and hypnotic in the treatment of insomnia, neuroses, and behavioural disorders. The use of bromides is generally deprecated (see p. 2460.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Onyric; *Spain*: Psicosoma.

Multi-ingredient Preparations. *Chile*: Gamalate B6; Gamavit B6; *Spain*: Gamalate B6; Psicosoma; *Ukr.*: Gamalate B6 (Гамалате B6).

Malabar Nut

Adhatoda; Adotodai; Adulsa; Arusa; Malabar Nut Tree; Malabarnöt; Malabarnuss; Pavettia; Vasaca; Vasaka.
CAS — 6159-55-3 (vasicine).
ATC Herb — HR03BB5003 (Justicia adhatoda: leaf); HR05WA5019 (Justicia adhatoda: leaf).
UNII — 9GL9VCO10F (Justicia adhatoda); HH159XOVB1 (Justicia adhatoda leaf); 3J544964HZ (Justicia adhatoda root).

Pharmacopoeias. *US* includes a monograph for Malabar-Nut-Tree Leaf and the powdered form and powdered extract.

USP 36: (Malabar-Nut-Tree, Leaf). The dried leaves of *Justicia adhatoda* (*Adhatoda vasica*) (Acanthaceae). It contains not less than 0.6% of vasicine, calculated on the dried basis. Protect from light and moisture.

Profile

The leaves, flowers, and roots of the malabar nut, *Justicia adhatoda* (*Adhatoda vasica*; *A. zeylanica*) Acanthaceae, are used in Indian traditional medicine, mainly as an expectorant and antispasmodic in preparations for cough and other respiratory-tract disorders. The principal constituents are adhatodic acid and the alkaloid vasicine (peganine).

Homoeopathy
Malabar nut has been used in homoeopathic medicines under the following names: Adhatoda vasica; Justicia; Justicia adhatoda.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: PulmaCo; *India*: Aglotus; Arjin; Arthopack; Arthopack; Astha; Astha; Diakof; Evecare; Evecaré; FN-T-Tus†; Geriforte; Geriforte; Haleezy; Honitus; Kof-Rid; Kofarest-H; Koflet; Leuko-G; Livomyn; Livomyn; Lukol; Myron; *Malaysia*: Strepsils Cough Lozenge†; Strepsils Cough Syrup†; *NZ*: Lice Blaster; *Rus.*: Doktor Mom (Доктор Мом); Insti (Инсти); Linkus (Линкас); Linkus Lor (Линкас Лор); Suprima-Broncho (Суприма-бронхо); Travisil (Трависил); *Singapore*: Claricof; Strepsils Cough Lozenge (with natural herbs); Strepsils Cough Syrup†; *Swed.*: Kan Jang; *Ukr.*: Bronchomed (Бронхомед); Doctor Cough (Доктор Кашель); Doktor Mom (Доктор Мом сироп); Eve Care (Ив Кер)†; Imunin (Иммунин)†; Insti (Інсті); Linkus (Линкас); Olesan (Олесан)†; Olesan (Олесан); Travisil (Трависил).

Homoeopathic Preparations. *Ger.*: Klosterfrau Allergin; Syxyl Heuschnupfen.

Malic Acid

Acide Malique; Ácido de las manzanas; Ácido hidroxisuccínico; Acidum Malicum; Acidum Malicum Racemicum; Äpfelsäure; Äppelsyra; Apple Acid; E296; Hydroxysuccinic Acid; Kyselina jablečná racemická; Málico, ácido; Obuolių rūgštis; Omenahappo; Яблочная Кислота.
(2*RS*)-2-Hydroxybutanedioic acid.
$C_4H_6O_5=134.1$
CAS — 6915-15-7 (malic acid); 636-61-3 ((+)-malic acid); 97-67-6 ((-)-malic acid); 617-48-1 ((±)-malic acid).
UNII — 817L1N4CKP ((±)-malic acid); J3TZF807X5 ((-)-malic acid).

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

Ger. also includes the *S*-form ((-)-malic acid).

Ph. Eur. 8: (Malic Acid). A white or almost white, crystalline powder. Freely soluble in water and in alcohol, sparingly soluble in acetone.

USNF 31: (Malic Acid). A white or practically white, crystalline powder or granules. Very soluble in water; freely soluble in alcohol.

Profile

Malic acid is used in pharmaceutical formulations as an acidifier, flavour, and as an alternative to citric acid in effervescent powders. It is used with butylated hydroxytoluene as an antoxidant in vegetable oils. It is used topically with benzoic acid and salicylic acid for desloughing of ulcers, burns, and wounds, and systemically with arginine (p. 2049.1) in preparations for the treatment of liver disorders. Pastilles containing malic acid are also used in the management of dry mouth (p. 2175.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Acerbine; Leberinfusion; *Chile*: Secand; *Cz.*: Ringerfundin; *Denm.*: Ringerfundin; *Fin.*: Ringerfundin; Xerodent; *Fr.*: Isofundine; Squaphane; SST†; *Hung.*: Egaver Plusz; Egaver; *Indon.*: Aviter; Viusid; *Ital.*: Keraflex; Sterofundin; *Neth.*: Sterofundin Iso; *Norw.*: Ringerfundin; Xerodent; *Rus.*: Hepasol A (Гепасол A); *S.Afr.*: Aserbine; *Singapore*: Bio-Taches†; *Spain*: Acerbiol†; *Swed.*: Ringerfundin; Xerodent; *Switz.*: Ringerfundin; *UK*: Hydrotab; Salivix; SST; *Ukr.*: Acerbin (Ацербин); Hepasol A (Гепасол A); *USA*: Saliva-Sure; *Venez.*: Lecivar Plus; Viusid.

Homoeopathic Preparations. *Ger.*: Hepar comp; Zitronensaurezyklus-Heel.

Mallow

Erdei mályvavirág (mallow flower); Květ slézu lesního (mallow flower); Liść ślazu (mallow leaf); Malvablomma (mallow flower); Malvae folium (mallow leaf); Malvae sylvestris flos (mallow flower); Malvenblätter (mallow leaf); Malvenblüten (mallow flower); Mauve des Bois (*Malva silvestris*); Mauve, feuille de (mallow leaf); Mauve, fleur de (mallow flower); Metsämalvankukka (mallow flower); Miškinių dedešvų žiedai (mallow flower); Мальва Лесная (*Malva sylvestris*); Просвирник Лесной (*Malva sylvestris*).
ATC Herb — HD02WA5003 (Malva sylvestris: seed); HA16AX5003 (Malva sylvestris: leaf); HA01WB5003 (Malva sylvestris: flower); HR05WA5027 (Malva sylvestris: leaf); HN02BG5007 (Malva sylvestris: seed); HR05WA5026 (Malva sylvestris: flower).

Pharmacopoeias. *Eur.* (see p. vii) includes Mallow Flower and Mallow Leaf.

Ph. Eur. 8: (Mallow Flower; Malvae sylvestris flos). The whole or fragmented dried flower of *Malva sylvestris* or its cultivated varieties. Protect from light.

Ph. Eur. 8: (Mallow Leaf; Malvae Folium). The whole or fragmented dried leaf of *Malva sylvestris*, *M. negleita*, or a mixture of both species. Protect from light.

Profile

Mallow flower and leaf act as demulcents and are ingredients of herbal remedies for coughs and cold symptoms. Mallow flower is used to enhance the colour of herbal teas and other foodstuffs. Mallow is also included in herbal remedies for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Malvatrikids Baby; *Cz.*: Slezovy Kvet†; *Ital.*: Malvina; *Switz.*: Tisane contre le toux irritative.

Multi-ingredient Preparations. *Arg.*: Acnetrol; Aristaloe; KW; Lactoscrub; Maprosol Gel; Mictasol Azul; Prurigel; Xyloprocto Toallas; *Austral.*: Neo-Cleanse; *Austria*: Midro Tee; *Belg.*: Mictasol; *Braz.*: Malvatricin Natural Soft†; Malvatricin Pastilhas; Malvatricin Pronto; Malvatricin Solucao para diluir; Malvatricin Spray; Malvatrikids F; Malvatrikids Junior; Malvodon†; Mictasol; *Canad.*: Bilonat; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; *Fr.*: Angiodrop; Apaisance†; Boribel Tisane No 13†; Erygine†; Mediflor Hepatique No 5; Mediflor Pectorale d'Alsace no 8†; Mucogyne; Pectoflorine†; Santane C_4†; Santane O1; Santane O1; Saugella Girl; Tisane Saint-Urbain†; Veganix; Yerbalaxa; *Hung.*: Telma; *Israel*: Midro-Tea; *Ital.*: Alkagin; Cistefi; Dentaton; Fito Stomygen†; Gliceroiax; Iridil; Microclismi Marco Viti†; Mictasone†; Neoderma 47; Nevril; Ninfagin; Perfluxi Cremagel; Piodermina; Plurilac; *Port.*: Alkagin; Alkagin; Alkagin; *Rus.*: Herbion Plantain Syrup (Гербион Сироп Подорожника); *Singapore*: Arkopharma Propolis Spray; *Switz.*: Malveol; *UK*: Spotner; *Ukr.*: Herbion Plantaginis Syrup (Гербион Сироп Подорожника).

Homoeopathic Preparations. *Canad.*: Common Mallow Combination†; Goldenrod Combination†.

Malotilate *(USAN, rINN)*

Malotilato; Malotilatum; NKK-105; Малотилат.
Diisopropyl 1,3-dithiole-$\Delta^{2\alpha}$-malonate.
$C_{12}H_{16}O_4S_2=288.4$
CAS — 59937-28-9.
UNII — RV59PND975.

Profile

Malotilate is used for a protective effect on liver function in patients with chronic hepatic disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Xin Yi Gan (辛益甘); Ya Bao Xin (亚宝欣); *Jpn*: Kantec.

Mannose Triflate

Tetraacetyl Mannose Triflate.
1,3,4,6-Tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose.
$C_{15}H_{19}F_3O_{12}S=480.4$
CAS — 92051-23-5.
UNII — 0KI8FFQ6TT.

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

Ph. Eur. 8: (Tetra-*O*-acetyl-mannose Triflate for Radiopharmaceutical Preparations). A white or almost white crystalline hygroscopic powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane; very soluble in acetonitrile. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Mannose triflate is a synthetic carbohydrate used as a precursor in the production of fludeoxyglucose (^{18}F) injection (see p. 2224.1).

Manuka

New Zealand Tea Tree; Манука.

Profile

The oil of manuka (*Leptospermum scoparium*) is used for its antimicrobial properties as an alternative to melaleuca oil (p. 2551.1). It is also used in aromatherapy. Manuka honey has also been used as a wound dressing (p. 2072.2).

References.

1. Cooper RA, *et al.* The sensitivity to honey of Gram-positive cocci of clinical significance isolated from wounds. *J Appl Microbiol* 2002; 93: 857–63.
2. Cooper RA, *et al.* The efficacy of honey in inhibiting strains of Pseudomonas aeruginosa from infected burns. *J Burn Care Rehabil* 2002; 23: 366–70.
3. English HK, *et al.* The effects of manuka honey on plaque and gingivitis: a pilot study. *J Int Acad Periodontol* 2004; 6: 63–7.
4. Jull A, *et al.* Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008; 95: 175–82.
5. Mavric E, *et al.* Identification and quantification of methylglyoxal as the dominant antibacterial constituent of Manuka (Leptospermum scoparium) honeys from New Zealand. *Mol Nutr Food Res* 2008; 52: 483–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Antiac; Sinose.

Marjoram

Majoranae Herba; Marjolaine; Sweet Marjoram; Ziele majeranku; Майоран.

ATC Herb — HG04BW5024 (Origanum majorana: herb); HR05DB5008 (Origanum majorana: herb); HN06AW5004 (Origanum majorana: herb); HN02CW5002 (Origanum majorana: herb); HA03WX5003 (Origanum majorana: herb).

UNII — G9Z40ZYU6P (Origanum majorana top); R40XM3HU5X (Origanum majorana).

NOTE. Distinguish from wild marjoram (see Oregano, p. 2576.3).

Pharmacopoeias. In *Pol.*

Profile

The dried leaves and flowers of marjoram, *Origanum majorana* (*Majorana hortensis*) (Lamiaceae), and the essential oil obtained from them have antibacterial properties. They are used, either separately or in combination, in herbal remedies for a variety of disorders. Marjoram is also used as a culinary herb.

Marjoram oil is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Menodoron; *Fr.*: Dystolise; *Ger.*: Menodoron; *Hung.*: Antipoll; Herbalakt; *Neth.*: Luuf Verkoudheidsbalsem (voor baby's); *Pol.*: Salviasept; *Port.*: Erpecalm; *Rus.*: Urolesan (Уролесан); *S.Afr.*: Menodoron†; *Switz.*: Menodoron.

Homoeopathic Preparations. *Cz.*: Hormeel S; *Fr.*: Boripharm No 41; *Hung.*: Hormeel S; *Rus.*: Hormeel SN (Гормель СН).

Marsh Tea

Crystal Tea; Ledi palustris herba; Lédon des marais; Marsh Cistus; Marsh Labrador Tea; Sumpf-Porst; Sumpfporstkraut; Wild Rosemary.

ATC Herb — HD11AX5002 (Ledum palustre: herb); HR05WA5022 (Ledum palustre: herb).

UNII — 877L01IZ0P.

NOTE. The names James' Tea and Labrador Tea have been applied to marsh tea (*Ledum palustre*) but are also used for the related species *L. groenlandicum* (*L. latifolium*; *Rhododendron groenlandicum*).

Although the synonym Wild Rosemary has been used for Marsh Tea, Rosemary (p. 2607.2) is an unrelated plant.

Profile

The dried aerial parts of marsh tea, *Ledum palustre* (*L. tomentosum*; *Rhododendron tomentosum*; *R. palustre*) (Ericaceae) have been used in herbal preparations mainly for rheumatic and respiratory tract disorders. It contains an irritant essential oil and has been abused as an abortifacient.

Homoeopathy

Marsh tea has been used in homoeopathic medicines under the following names: Ledum; Ledum palustre.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Joint & Muscle Cream; *Cz.*: Cicaderma; *Ger.*: Rhus-Rheuma-Gel N; *Mex.*: Sanicut; *Port.*: Cicaderma; *Rus.*: Pectorales Species No 4 (Грудной Сбор 4).

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Joint & Muscle Oral Spray†; Sports Ice Joint & Muscle; *Austria*: Ledum Med Complex; Proagil; Rhus Med Complex; Thuja Med Complex; *Canad.*: Adrisin†; Arnicaid; Cicaderma†; Cutisitum†; Hylands LCQ; Hylands Leg Cramps; Rudistrol†; Toxex; *Chile*: Artroplex; *Fr.*: Abbe Chaupitre no 13; Abbe Chaupitre no 23†; Cicaderma; Ledum Complexe No 81; Urtica Complexe No 82†; *Ger.*: Anore rheumat; Arthrokatt; Arthrorell N; Berberis N Oligoplex; Bomarthros Harpagophytum Complex; Colchicum Complex; Doloject; G1-Injektopas; Hewerheum N†; Homvioartrin; Rheucostan R; Rheuma-Hevert; Rheuma-Hevert; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Steirocall S†; *Neth.*: Arnilite; Homeocare Exercito; Kruidvat Homeopathie Bzzz†; Kruidvat Homeopathie Spier- en gewrichtsgel†; Prrrikweg; Prurilite; Rudistrol†; Spiroflor; Urtizon complex; *Rus.*: Cicaderma (Цикадерма); Rewma-Gel (Ревма-Гель); *Switz.*: Omida Gel Antirhumatismal; Regenaplex Nr. 21c; *UK*: Pyrethrum Spray; *Ukr.*: Reuma-Gel (Ревма-Гель).

Mastic

Almáciga; Mastiche; Mastiksi; Mastix; Pistacijų mastika; Мастика.

ATC Herb — HA01AD5002 (Pistacia lentiscus: resin).

UNII — 7446H202QW.

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

Ph. Eur. 8: (Mastic). The dried resinous exudate obtained from stems and branches of *Pistacia lentiscus* var. *latifolius*. It contains a minimum of 1% v/w of essential oil, calculated with reference to the anhydrous drug. It should not be powdered.

Profile

Solutions of mastic in alcohol, chloroform, or ether have been used, applied on cotton wool, as temporary fillings for carious teeth. Compound Mastic Paint (BP 1980) was formerly used as a protective covering for wounds and to hold gauze in position.

Mastic gum has been used in the management of peptic ulcer disease.

Peptic ulcer disease. Mastic has traditionally been used in the treatment of gastrointestinal disorders such as peptic ulcer. It has been suggested that any effect may be related to its *in vitro* activity against *Helicobacter pylori*[1,2] and although one small study[3] found that it had little effect on the load of *H. pylori in vivo*, a later study sponsored by the manufacturers produced somewhat more encouraging results.[4]

1. Huwez FU, *et al.* Mastic gum kills Helicobacter pylori. *N Engl J Med* 1998; 339: 1946. Correction. *ibid.*:340: 576 [dose].
2. Paraschos S, *et al.* In vitro and in vivo activities of Chios mastic gum extracts and constituents against Helicobacter pylori. *Antimicrob Agents Chemother* 2007; 51: 551–9.
3. Bebb JR, *et al.* Mastic gum has no effect on Helicobacter pylori load in vivo. *J Antimicrob Chemother* 2003; 52: 522–3.
4. Dabos KJ, *et al.* The effect of mastic gum on Helicobacter pylori: a randomized pilot study. *Phytomedicine* 2009. Available at: doi: 10.1016/j.phymed.2009.09.010

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Mastika†.

Meadowsweet

Algört; Filipendulae Ulmariae Herba; Mädesüsskraut; Mesiangervo; Nať tužebníku jilmového; Pelkinių vingiorykščių žolė; Queen of the Meadows; Reina de los prados; Reine des Prés; Reine des prés, sommité fleurie de; Spiraeae Herba; Ulmaria; Лабазник; Таволга.

ATC Herb — HJ01WB5008 (Filipendula ulmaria: herb); HA16AX5002 (Filipendula ulmaria: herb); HR05YA5007 (Filipendula ulmaria: flower); HG04BW5012 (Filipendula ulmaria: flower); HN02BA5001 (Filipendula ulmaria: herb).

UNII — 3LH0M209LN (Filipendula ulmaria); 06L18L32G6 (Filipendula ulmaria flower); 7495ZGS5HI (Filipendula ulmaria flowering top); 37GVN739ZQ (Filipendula ulmaria leaf); 997724QNDS (Filipendula ulmaria root).

NOTE. The name Queen of the Meadow has also been applied to Gravel Root (p. 2522.1).

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

Ph. Eur. 8: (Meadowsweet). The whole or cut, dried flowering tops of *Filipendula ulmaria* (*Spiraea ulmaria*). It contains a minimum of 0.1% v/w of essential oil (dried drug). It has an aromatic odour of methyl salicylate after crushing.

Profile

Meadowsweet is used in herbal medicine as a diuretic and in gastrointestinal and rheumatic disorders.

Homoeopathy

Meadowsweet has been used in homoeopathic medicines under the following names: Filipendula ulmaria; Spiraea; Spiraea ulmaria; Spiraea ulmaria ex herba; Filip. ul.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Detox Program; Digestive Bitters; HiPep; *Canad.*: Cellutex; *Cz.*: Antirevmaticky Caj†; *Fr.*: Arthritisane†; Arthroflorine†; Chondrosteo; Dolores; Drainuryl; Fibromyalgine; Hydracur; Mediflor Diuretique No 4†; Mediflor Douleurs Articulaires no 2†; OM3flex†; Santane A_4†; Santane O1; Santane R_8†; Tisane de Sante†; Tisane Provencale no 2†; Tisane Provencale no 6†; *Ital.*: Flodolor; Lik-Gel†; Neuralta Migren; Pik Gel; *Mex.*: Rodan; *Mon.*: Algicuivre; *Pol.*: Infektoten†; Reumaherb; *Switz.*: Urinex; *UK*: Acidosis; Acidosis; Indigestion Mixture; Pure Plan; *Ukr.*: Tazalok (Тазалок); *USA*: Amerigel.

Homoeopathic Preparations. *Cz.*: Ferrum Homaccord†; *Fr.*: Urodren; *Ger.*: Colchicum Complex; Gelenk Albin; Hewerheum N†; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Rheuma-Hevert†; Rheuma-Hevert; Rheuma-Hevert; Rheumeda; *Neth.*: Phonix Solidago comp; Rhodolith-Gastreu R46; *Ukr.*: Homvio-Reuman (Хомвио-Ревман).

Meclofenoxate Hydrochloride

(BANM, rINNM) ⊗

Centrophenoxine Hydrochloride; Clofenoxine Hydrochloride; Clophenoxate Hydrochloride; Deanol 4-Chlorophenoxyacetate Hydrochloride; Hidrocloruro de meclofenoxato; Meclofenoxane Hydrochloride; Méclofénoxate, Chlorhydrate de; Meclofenoxati Hydrochloridum; Meclofenoxato, hidrocloruro de; Меклофеноксата Гидрохлорид.

2-Dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride.

$C_{12}H_{16}ClNO_3,HCl=294.2$

CAS — 51-68-3 (meclofenoxate); 3685-84-5 (meclofenoxate hydrochloride).

ATC — N06BX01.

ATC Vet — QN06BX01.

UNII — 5BK3070BDY.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Meclofenoxate hydrochloride has been claimed to aid cellular metabolism in the presence of diminished oxygen concentrations. It has been given mainly for mental changes in the elderly, or after strokes or head injury.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Lucidril.

Meglumine *(BAN, rINN)*

Meglumiini; Meglumin; Meglumina; Megluminas; Méglumine; Megluminum; Меглюмин.

N-Methylglucamine; 1-Methylamino-1-deoxy-D-glucitol.

$C_7H_{17}NO_5=195.2$

CAS — 6284-40-8.

UNII — 6HG8UB2MUY.

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

Ph. Eur. 8: (Meglumine). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane.

USP 36: (Meglumine). White to faintly yellowish-white, odourless crystals or powder. Freely soluble in water; sparingly soluble in alcohol.

Profile

Meglumine is an organic base used for the preparation of salts of organic acids including many used as contrast media.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Contrastin; *Rus.*: Remaxol (Ремаксол).

Melaleuca Oil

Australian Tea Tree Oil; Melaleuca, aceite de; Melaleuca, huile essentielle de; Melaleucae Aetheroleum; Melaleucae Etheroleum; Mirteniu eterinis aliejus; Oleum Melaleucae; Silice kajeputu stridavolistého; Tea Tree Oil; Teebaumöl; Teepuuöljy; Tetrádolja; Масло чайного Дерева.

CAS — 68647-73-4; 8022-72-8.

ATC Herb — HD08AW5001 (Melaleuca alternifolia: essential oil); HA03AW5035 (Melaleuca leucadendra: essential oil); HP03AX5001 (Melaleuca leucadendra: essential oil); HM02AW5008 (Melaleuca leucadendra: essential oil); HP03BX5003 (Melaleuca leucadendra: essential oil); HR05WA5029 (Melaleuca leucadendra: essential oil).

UNII — VIF565UC2G.

NOTE. Though the synonym Ti-tree Oil has been used for melaleuca oil (e.g. in BPC 1949), the name Ti-tree is also applied to species of *Cordyline* (Liliaceae) indigenous to New Zealand.

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

Ph. Eur. 8: (Tea Tree Oil). The essential oil obtained by steam distillation from the foliage and terminal branchlets of *Melaleuca alternifolia, M. linariifolia, M. dissitiflora*, and/or other species of *Melaleuca*. It contains less than 7.0% aromadendrene, less than 15% cineole, 0.5 to 12.0% *p*-cymene, 0.5 to 4.0% limonene, 1.0 to 6.0% α-pinene, less than 3.5% sabinene, 5.0 to 13.0% α-terpinene, 10.0 to 28.0% γ-terpinene, minimum of 30% terpinen-4-ol, 1.5 to 8.0% α-terpineol, and 1.5 to 5.0% terpinolene.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Melaleuca oil has bactericidal and fungicidal properties and is used topically for various skin disorders. It is also used in aromatherapy.

References.

1. Carson CF, *et al.* Efficacy and safety of tea tree oil as a topical antimicrobial agent. *J Hosp Infect* 1998; **40:** 175–8.
2. Allen P. Tea tree oil: the science behind the antimicrobial hype. *Lancet* 2001; **358:** 1245.
3. Satchell AC, *et al.* Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol* 2002; **43:** 175–8.
4. Hammer KA, *et al.* In vitro activity of Melaleuca alternifolia (tea tree) oil against dermatophytes and other filamentous fungi. *J Antimicrob Chemother* 2002; **50:** 195–9.
5. Satchell AC, *et al.* Treatment of dandruff with 5% tea tree oil shampoo. *J Am Acad Dermatol* 2002; **47:** 852–5.
6. Koh KJ, *et al.* Tea tree oil reduces histamine-induced skin inflammation. *Br J Dermatol* 2002; **147:** 1212–7.
7. Mozeiso NB, *et al.* Immediate systemic hypersensitivity reaction associated with topical application of Australian tea tree oil. *Allergy Asthma Proc* 2003; **24:** 73–5.
8. Perrett CM, *et al.* Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; **28:** 167–70.
9. Hammer KA, *et al.* Antifungal effects of Melaleuca alternifolia (tea tree) oil and its components on Candida albicans, Candida glabrata and Saccharomyces cerevisiae. *J Antimicrob Chemother* 2004; **53:** 1081–5.
10. Hammer KA, *et al.* A review of the toxicity of Melaleuca alternifolia (tea tree) oil. *Food Chem Toxicol* 2006; **44:** 616–25.
11. Carson CF, *et al.* Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev* 2006; **19:** 50–62.

For a disputed association between products containing melaleuca and lavender oils and the development of prepubertal gynaecomastia, see under Lavender Oil, p. 2541.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Clean Skin Anti Acne†; Moov Insect Repellent; Rapaid Itch Relief; *Chile*: Acnoxyl Acondicionador; Sebolic; *Fr.*: Myleuca; *Hung.*: Tebamol; *Irl.*: MOOV Head Lice†; *Israel*: Burnshield; *Malaysia*: MOOV; *Mon.*: Onykoleine; *Singapore*: Moov; Rapaid; *UK*: Burnshield Gel; Melavir; Vosene Kids 3 in 1.

Multi-ingredient Preparations. *Arg.*: Sebosoap; *Austral.*: Apex Repel Natural; Bosisto's Antiseptic Spray; Clean Skin Face Wash†; Elmore Oil; Moov Head Lice Solution; NeutraLice; Nyal Nasal Spray; Rapaid Rash-Relief; *Chile*: Acnoxyl Abrasivo†; Acnoxyl Gel Humectante; Acnoxyl Jabon Liquido†; Acnoxyl Locion Tonica; *Fr.*: Cicatridine; Esculape†; Mycogel†; Navi Blef; Olioseptil Gorge-Larynx; Olioseptil Nez-Gorge; Phytosquame†; Squaphane P; *Hong Kong*: Mycogel†; Vita Coldycin Echinacea Plus†; *India*: Acneguard; Acnestal; Climdan; Clin-3; Dandruff Plus; Evaren; LTT Cleanser; Moiste; *Irl.*: Skin Clear†; *Israel*: Acti Talc; *Ital.*: Keromicil; Keromicil; Naturocil; Vaginol; *Malaysia*: T3 Acne; *NZ*: Electric Blue Headlice; Electric Blue Headlice; Lice Blaster; *Philipp.*: Enfacare; *Singapore*: Burnaid; Purifying Gel; Rapaid; Regulator; T3; Teenstick; *Thai.*: Fungicon; Gynecon-T; *UK*: Dr Johnsons Nit & Lice; Sinose; Skin Clear; Tea Tree & Witch Hazel Cream; Teenstick; *USA*: Zim's Max Freeze.

Melanocyte-stimulating Hormone

B Hormone; Chromatophore Hormone; Hormona melanocitoestimulante; Intermedin; Intermedina; Melanotropin; Melanottopina; MSH; Pigment Hormone; Меланоцитостимулирующий Гормон.

CAS — 9002-79-3.

Profile

Melanocyte-stimulating hormone is a polypeptide isolated from the pars intermedia of the pituitary of fish and amphibia which causes dispersal of melanin granules in the skin of fish and amphibia and allows adaptation to the environment.

In adult humans, the pituitary gland lacks a distinct intermediate lobe, and the pituitary is not thought to secrete melanocyte-stimulating hormone (MSH) directly. However, the precursor molecule, pro-opiomelanocortin, is cleaved in the pituitary into corticotropin (p. 1628.3), the glycoprotein β-lipotrophin (β-LPH), and an amino-terminal peptide. Subsequent processing in other tissues, such as the brain and gastrointestinal tract, may yield three forms of MSH: α-MSH (via corticotropin cleavage), β-MSH, and γ-MSH. The presence and function of these melanocyte-stimulating hormones in man are uncertain. A receptor analogous to that in amphibians is apparently lacking in humans; effects on skin pigmentation emanating from the pituitary are mainly mediated by corticotropin.

Release of melanocyte-stimulating hormone is inhibited in *animals* by melanostatin; there is also evidence for a hypothalamic releasing factor (MRF).

Melanocyte-stimulating hormone is under investigation, as α-MSH, in the prevention and treatment of ischaemic intrinsic acute renal failure. Afamelanotide (4-L-norleucine-7-D-phenylalanine-α-MSH; melanotan-I), a synthetic analogue of α-MSH, is under investigation as a photoprotective agent in skin conditions such as erythropoietic protoporphyria, phototoxicity associated with photodynamic therapy, polymorphous light eruptions, actinic keratosis, and solar urticaria. Another α-MSH synthetic analogue, melanotan-II, was under investigation for sexual dysfunction although this has been abandoned. However, its metabolite, bremelanotide (PT-141), is under investigation for haemorrhagic shock. Afemelanotide and melanotan II are widely abused as lifestyle drugs (see below).

Abuse. Analogues of α-melanocyte-stimulating hormone (α-MSH) are illicitly manufactured and supplied as lifestyle drugs. Afamelanotide (melanotan I) is widely abused to obtain a cosmetic tan. Some people also use it for medical conditions such as rosacea and fibromyalgia. Another α-MSH analogue, melanotan II, is abused to increase sexual desire and induce penile erections.[1] Illicit supply and use of such drugs raises several concerns.[1,2] The safety, quality, and efficacy of unregulated compounds is always questionable and there is the additional concern of sterility of the preparation since α-MSH analogues are reconstituted in bacteriostatic water and given by subcutaneous injection. Endogenous α-MSH has many regulatory functions in humans and therefore use of exogenous α-MSH analogues could adversely affect several physiological systems, especially as there is the potential for long-term use if abused for lifestyle reasons. Illicit use of α-MSH for tanning has also been associated with a change in size and pigmentation of pre-existing moles[3] and a rapid increase in the number of new moles.[4,5]

1. Evans-Brown M, *et al.* Use of melanotan I and II in the general population. *BMJ* 2009; **338:** 424–5.
2. MHRA. "Tan jab" is an unlicensed medicine and may not be safe — warns medicines regulator. Press release (issued 17 November 2008). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON031009 (accessed 04/06/09)
3. Langan EA, *et al.* Change in moles linked to use of unlicensed "sun tan jab". *BMJ* 2009; **338:** 251.
4. Cardones AR, Grichnik JM. α-Melanocyte-stimulating hormone-induced eruptive nevi. *Arch Dermatol* 2009; **145:** 441–4.
5. Cousen P, *et al.* Eruptive melanocytic naevi following melanotan injection. *Br J Dermatol* 2009; **161:** 707–8.

Erythropoietic protoporphyria. Afamelanotide as a modified-release resorbable implant given subcutaneously at a dose of 20 mg and repeated after an interval of 60 days has shown benefit in the treatment of erythropoietic protoporphyria in 5 patients in an open-label study.[1]

1. Harms J, *et al.* An α-melanocyte-stimulating hormone analogue in erythropoietic protoporphyria. *N Engl J Med* 2009; **360:** 306–7.

Melanostatin

Hormona inhibidora de la melanotropina; Intermedin-inhibiting Factor; Melanocyte-stimulating-hormone-release-inhibiting Factor; Melanostatina; Melanotropin Release-inhibiting Factor; MIF; Меланостатин.

Pro-Leu-Gly-NH_2.

CAS — 9083-38-9.

Profile

Melanostatin is a tripeptide, obtained from the hypothalamus, that inhibits the release of melanocyte-stimulating hormone (see above) in *animals*. However, there is little evidence of its activity in man. It has been tried in the treatment of depression and parkinsonism but with little benefit.

Melatonin

N-Acetyl-5-methoxytryptamine; Melatoniini; Melatonina; Melatoninum.

N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide.

$C_{13}H_{16}N_2O_2$=232.3

CAS — 73-31-4.

ATC — N05CH01.

ATC Vet — QN05CH01.

UNII — JL5DK93RCL.

Pharmacopoeias. In *Br* and *US*.

BP 2014: (Melatonin). A white to off-white crystalline powder. Slightly soluble in water; soluble in methyl alcohol, in acetone, and in ethyl acetate. Store at a temperature not exceeding 30 degrees. Protect from light.

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

Uses and Administration

Melatonin is a hormone produced in the pineal gland from the amino acid tryptophan. Results mainly from *animal* studies indicate that melatonin increases the concentration of aminobutyric acid and serotonin in the midbrain and hypothalamus and enhances the activity of pyridoxal-kinase, an enzyme involved in the synthesis of aminobutyric acid, dopamine, and serotonin. Melatonin is involved in the inhibition of gonadal development and in the control of oestrus. It is also involved in protective changes in skin coloration. There appears to be a diurnal rhythm of melatonin secretion; it is secreted during hours of darkness and may affect sleep pattern. Because of its possible role in influencing circadian rhythm, melatonin has been tried in the alleviation of jet lag and other disorders resulting from delay of sleep. Melatonin is given orally as a modified-release preparation in doses of 2 mg once daily, 1 to 2 hours before bedtime and after food, for the short-term management of primary insomnia in patients aged 55 or over; the dosage may be continued for up to 13 weeks. Melatonin has also been studied in various depressive disorders including seasonal affective disorder, and in large doses for its contraceptive activity.

For doses in children, see p. 2552.1.

Several melatonin analogues are being developed.

Melatonin has been tried in several disorders[1] including, in large doses, as an adjunct to conventional chemotherapy for malignant neoplasms[2,3] and, with norethisterone, as a contraceptive.[4] It is possible that contraceptive use of melatonin may be associated with a reduced risk of breast cancer.[5] For mention of response to melatonin in 2 patients with sarcoidosis, see p. 1612.2. Preliminary studies have also suggested that melatonin may be beneficial in hyperlipidaemias,[6] cluster headaches,[7] tinnitus,[8] alopecia in women,[9] and irritable bowel syndrome associated with sleep disturbances.[10] Repeated bedtime doses may also play a part in reducing nocturnal blood pressure in patients with essential hypertension.[11] Claims for its value as an anti-ageing treatment and for use in conditions such as Alzheimer's disease and AIDS are unfounded.[2,12] The effects of long-term use of melatonin have yet to be assessed.

1. Wetterberg L. Melatonin and clinical application. *Reprod Nutr Dev* 1999; **39:** 367–82.
2. Pepping J. Melatonin. *Am J Health-Syst Pharm* 1999; **56:** 2520–7.
3. Lissoni P, *et al.* Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer* 1999; **35:** 1688–92.
4. Short RV. Melatonin. *BMJ* 1993; **307:** 952–3.
5. Cohen M, *et al.* Hypotheses: melatonin/steroid combination contraceptives will prevent breast cancer. *Breast Cancer Res Treat* 1995; **33:** 257–64.
6. Pittalis S, *et al.* Effect of a chronic therapy with the pineal hormone melatonin on cholesterol levels in idiopathic hypercholesterolemic patients. *Recenti Prog Med* 1997; **88:** 401–2.
7. Leone M, *et al.* Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996; **16:** 494–6.

8. Rosenberg SI, *et al.* Effect of melatonin on tinnitus. *Laryngoscope* 1998; 108: 305–10.
9. Fischer TW, *et al.* Melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia: results of a pilot randomized controlled trial. *Br J Dermatol* 2004; 150: 341–5.
10. Song GH, *et al.* Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. *Gut* 2005; 54: 1402–7.
11. Scheer FAJL, *et al.* Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004; 43: 192–7.
12. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997; 336: 186–95.

Administration in children. Although melatonin is unlicensed in the UK for use in children, the *BNPC* suggests that it may be used for the treatment of sleep-onset insomnia and delayed sleep phase syndrome associated with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, autism, and learning difficulties in children aged 1 month to 18 years. Suggested oral doses are 2 to 3 mg once daily initially, increased if necessary after 1 to 2 weeks to 4 to 6 mg up to a maximum of 10 mg daily. However, little is known about the long-term effects of melatonin in children, including its effects on other circadian rhythms such as endocrine or reproductive hormone secretion, and use in children should therefore be reviewed every 6 months. Unlicensed immediate-release formulations of melatonin may be more suitable for use in children rather than the licensed modified-release formulation used in adults (see p. 2551.3), but in this case, prescribers should specify the manufacturer because of variability in clinical effect between unlicensed preparations.

Melatonin is also sometimes used in children before magnetic resonance imaging (MRI), computed tomography (CT), or EEG investigations.

Insomnia. Although melatonin is considered[1-6] to be potentially useful in the management of various forms of insomnia (p. 1033.2), especially those associated with circadian rhythm disturbances, there is little evidence of efficacy from large studies[7] and its long-term safety is unknown. A meta-analysis[8] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency in secondary sleep disorders or those accompanying sleep restriction such as jet lag and shift work. In healthy subjects melatonin has been reported[9,10] to reduce the time to onset of sleep and to increase the time spent asleep. Whether this is due to adjustment of the 'body clock' or any hypnotic action of melatonin is unclear. Measurement of nocturnal urinary excretion of the major metabolite, 6-sulfatoxymelatonin, showed that low nocturnal melatonin production is associated with insomnia in patients over 55 years of age, and might identify those more likely to respond to treatment with melatonin.[11] Improved quality of sleep has been reported in elderly patients treated with melatonin for insomnia,[12] and it might be of use in delayed sleep phase syndrome[13] and insomnia in shift workers and totally blind people, although some[14,15] have found no beneficial effects of melatonin in night shift workers or emergency medicine employees. There has also been a report[16] of a patient with somnolence associated with melatonin deficiency after pinealectomy who responded to treatment with melatonin. A preliminary report[17] has suggested that use of melatonin may enable benzodiazepine therapy for insomnia to be stopped without impairing the quality of sleep. However, melatonin might adversely affect sleep patterns in some circumstances.[18] Melatonin has been tried with some benefit in improving sleep patterns in patients with end-stage renal disease undergoing daytime haemodialysis.[19] Transdermal melatonin may have advantages over fast-release oral formulations in improving plasma-melatonin concentrations.[20]

1. Haimov I, Lavie P. Potential of melatonin replacement therapy in older patients with sleep disorders. *Drugs Aging* 1995; 7: 75–8.
2. Brown GM. Melatonin in psychiatric and sleep disorders: therapeutic implications. *CNS Drugs* 1995; 3: 209–26.
3. Anonymous. Melatonin. *Med Lett Drugs Ther* 1995; 37: 111–12.
4. Arendt J. Melatonin. *BMJ* 1996; 312: 1242–3.
5. Lamberg L. Melatonin potentially useful but safety, efficacy remain uncertain. *JAMA* 1996; 276: 1011–14.
6. Skene DJ, *et al.* Use of melatonin in the treatment of phase shift and sleep disorders. *Adv Exp Med Biol* 1999; 467: 79–84.
7. Anonymous. Melatonin for primary insomnia? *Drug Ther Bull* 2009; 47: 74–7.
8. Buscemi N, *et al.* Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; 332: 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385.pdf (accessed 25/07/08)
9. Zhdanova IV, *et al.* Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther* 1995; 57: 552–8.
10. Attenburrow MEJ, *et al.* Low dose melatonin improves sleep in middle-aged subjects. *Psychopharmacology (Berl)* 1996; 126: 179–81.
11. Leger D, *et al.* Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *Am J Med* 2004; 116: 91–5.
12. Garfinkel D, *et al.* Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995; 346: 541–4.
13. Nagtegaal JE, *et al.* Effects of melatonin on the quality of life in patients with delayed sleep phase syndrome. *J Psychosom Res* 2000; 48: 45–50.
14. Wright SW, *et al.* Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. *Ann Emerg Med* 1998; 32: 334–40.
15. Jockovich M, *et al.* Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts. *Acad Emerg Med* 2000; 7: 955–8.
16. Lehmann ED, *et al.* Somnolence associated with melatonin deficiency after pinealectomy. *Lancet* 1996; 347: 323.
17. Garfinkel D, *et al.* Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999; 159: 2456–60.
18. Middleton BA, *et al.* Melatonin and fragmented sleep patterns. *Lancet* 1996; 348: 551–2.
19. Koch BC, *et al.* The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (RMSCAP study). *Br J Clin Pharmacol* 2009; 67: 68–75.
20. Aeschbach D, *et al.* Use of transdermal melatonin delivery to improve sleep maintenance during daytime. *Clin Pharmacol Ther* 2009; 86: 378–82.

Jet lag. Melatonin has been reported to alleviate jet lag after long flights.[1-5] The most appropriate dosing schedule has yet to be determined but will depend on both the direction of travel and the distance travelled. A systematic review[6] concluded that melatonin was effective in preventing or reducing jet lag in those travelling across 5 or more time zones, particularly in an easterly direction, and especially if jet lag had been experienced previously; travellers crossing 2 to 4 time zones might also derive benefit. However, a meta-analysis[7] of randomised controlled studies concluded that melatonin does not have a significant effect on sleep onset latency accompanying jet lag.

1. Waterhouse J, *et al.* Jet-lag. *Lancet* 1997; 350: 1611–16.
2. Arendt J. Jet-lag. *Lancet* 1998; 351: 293–4.
3. Arendt J. Jet-lag and shift work: (2) therapeutic use of melatonin. *J R Soc Med* 1999; 92: 402–5.
4. Waterhouse J, *et al.* Jet lag: trends and coping strategies. *Lancet* 2007; 369: 1117–29.
5. Sack RL. Jet lag. *N Engl J Med* 2010; 362: 440–7.
6. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2002 (accessed 28/04/05).
7. Buscemi N, *et al.* Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. Abridged version: *BMJ* 2006; 332: 385–8. Full version: http://www.bmj.com/cgi/reprint/332/7538/385.pdf (accessed 25/07/08)

Adverse Effects and Precautions

The most commonly reported adverse effects with melatonin are headache, nasopharyngitis, back pain, and arthralgia.

Melatonin should not be used in patients with autoimmune disease or hereditary galactose intolerance disorders, LAPP lactase deficiency, or glucose-galactose malabsorption. Melatonin should not be used in patients with hepatic impairment because of reports of decreased clearance in such patients.

Effects on the nervous system. An increase in seizure activity was noted in 4 of 6 children with severe neurological deficits during treatment with melatonin for sleep disorders.[1] Seizure activity returned to baseline values when melatonin was stopped and recurred on rechallenge.

1. Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998; 351: 1254.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies melatonin 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)

Interactions

Cytochrome P450 isoenzymes CYP1A1 and CYP1A2 are involved in the metabolism of melatonin and consequently other drugs that inhibit or induce these isoenzymes may affect melatonin levels. Melatonin should not be taken with fluvoxamine, methoxsalen, cimetidine, or oestrogens, all of which increase melatonin concentrations through inhibition of its metabolism. Tobacco smoking has been reported to decrease melatonin concentrations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Armonil Noche; Buenas Noches; Melatol; *Austral.*: Circadin; *Austria*: Circadin; *Belg.*: Circadin; *Cz.*: Circadin; *Denm.*: Circadin; *Fr.*: Circadin; *Ger.*: Circadin; *Gr.*: Circadin; *Hung.*: Bio-Melatonin; Circadin; *India*: Meloset; *Irl.*: Circadin; *Israel*: Circadin; *Ital.*: Armonia; Melamil†; *Mex.*: Benedorm; Cronocaps; Normolem; Remedin; *Neth.*: Circadin; *Norw.*: Circadin; *NZ*: Circadin; *Philipp.*: Sleepwell; *Pol.*: Circadin; *Port.*: Circadin; *Rus.*: Circadin (Циркадин); Melaxen (Мелаксен); *Spain*: Circadin; *Swed.*: Circadin; *Switz.*: Circadin; *Thai.*: Circadin; *UK*: Circadin; *Ukr.*: Melaxen (Мелаксен); *USA*: Transzone.

Multi-ingredient Preparations. *Arg.*: Plenovit Melatonina; *India*: Alprax Z; Destres; Eternex†; Meloprax; Stresnil; *Ital.*: Nervocel†; Pineal Notte; Pineal Notte; Stressout; *Philipp.*: Sleepasil; *USA*: Bevitamel; Melagesic PM; PowerSleep.

Pharmacopoeial Preparations
BP 2014: Melatonin Capsules;
USP 36: Melatonin Tablets.

Melilot

Barkūno žolė; Gelber Steinklee; Komonicová nať; Meliloť; Meliloti herba; Rohtomesikkä; Sötväppling; Steinkleekraut; Sweet Clover; Yellow Melilot; Yellow Sweet Clover; Ziele nostrzyka; Донник.

ATC Herb — HC05BW5002 (Melilotus officinalis: herb).
UNII — DJR90OLD7P (Melilotus officinalis); GM6P02J2DX (Melilotus officinalis top).

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

Ph. Eur. 8: (Melilot; Meliloti Herba). The whole or cut, dried aerial parts of *Melilotus officinalis*. It contains a minimum of 0.3% coumarin, calculated with reference to the dried drug. Protect from light.

Profile

Melilot is used internally in herbal preparations for chronic venous insufficiency. It contains coumarin (see p. 2487.2) and its derivatives, and the dose may be expressed in terms of coumarin. The German expert committee for herbal drugs and preparations (Commission E) also allows the addition or substitution of *M. altissimus* (tall melilot), tall yellow sweet clover.

Melilotus officinalis is also used externally.

Homoeopathy

Melilot has been used in homoeopathic medicines under the following names: Melilotus officinalis; Melilotus off; Mel. off.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Varizil; Vecasten; Venolise; *Ger.*: Meli Rephastasan†; *Ital.*: Linfodermina.

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; Cellasene†; Gentianella; Snell Patch; Snell Progress; Varicura; Venart Crema; *Austral.*: Zellulean with Escin†; *Canad.*: Natraway Sport 1 & 2†; *Chile*: Celltech; *Fr.*: Anthylline†; Antinerveux Lesourd†; Creme au Melilot Composee†; Cyclo 3; Esberiven Fort; Esberiven; Evarose†; Mediflor Circulation du Sang No 12†; Santane V_3†; Sedopal; *Ital.*: Binfolipase; Binfonorm†; Capill Venogel; Cumadren; Deproctol; Dermilia Flebozin†; Deroidal; Diosmina Complex; Facosmina; Flebo-Si†; Flebofort; Flebonorm; Flebovis materna; Flebovis; Flebozin; Fraxiven; Gefion; Levital Plus; Linfoguard†; Linfonorm Cremagel; Lipaven; Pulsalux; Tractoven; Traumaven; Venodin; Venoplant; Venoplant; Venoton; *Pol.*: Masc na Odciski; Tabletki Tonizujace; *Rus.*: Cyclo 3 (Цикло 3); Herbion Aesculus (Гербион Эскулус); *Singapore*: Cyclo 3†; *Spain*: Fabroven†; *Switz.*: Phlebodril; *Ukr.*: Herbion Aesculus (Гербион Эскулус); Pravenor (Праенор).

Homoeopathic Preparations. *Austria*: Spigelon; Venodril; *Canad.*: Headache & Migraine L77; Headache & Migraine; Homeo-Form MI†; Nareel†; Spigelon†; *Fr.*: Hypericum Complexe No 26; Phapax; *Ger.*: Biodolor; Cefanalgin†; Neuro-Do; Pflugerplex Gelsemium; Schwoneural N; veno-loges N; *Hung.*: Naso-Heel S; Spigelon; *Neth.*: Aesculus Comp; Cephalite; Co-Hypert; Gynaelite; *Switz.*: Spigelon.

Melissa

Balm, Lemon; Citromfűlevél; Lemon Balm; Liść melisy; Meduňkový list; Melisų lapai; Melisa; Melissa; Melissae folium; Mélisse, feuille de; Melissenblatt; Sitruunamelissanlehti; Toronjil; Мелисса Лекарственная.

ATC Herb — HN02CW5001 (Melissa officinalis: leaf); HA03AW5036 (Melissa officinalis: leaf); HN05CM5015 (Melissa officinalis: leaf); HR05YA5013 (Melissa officinalis: leaf).
UNII — YF70189L0N (Melissa officinalis whole); 50D2ZE9219 (Melissa officinalis leaf).

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract prepared from the leaves.

Ph. Eur. 8: (Melissa Leaf). The dried leaf of *Melissa officinalis*. It contains not less than 1% of rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3), calculated with reference to the dried drug. It has an odour reminiscent of lemon. Protect from light.

Profile

Melissa has been used as a carminative and sedative. It is an ingredient of herbal remedies used for a variety of disorders. It is also reported to have virustatic activity and has been applied topically for herpes labialis. The chief constituent of

melissa is citral (p. 2480.2). Hypersensitivity reactions to melissa have been reported.

Melissa is the source of melissa oil (see below).

Homoeopathy

Melissa has been used in homoeopathic medicines under the following names: Melissa officinalis.

References.

1. Ballard CG, *et al.* Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with melissa. *J Clin Psychiatry* 2002; 63: 553–8.
2. WHO. Folium Melissae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/18.html (accessed 05/02/10)
3. Ulbricht C, *et al.* Natural Standard Research Collaboration. Lemon balm (*Melissa officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; 5: 71–114.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Lomaherpan; *Belg.*: Dormiplant†; *Canad.*: Herpecalm†; *Chile*: Citromel; *Cz.*: Medunkovy; *Ger.*: Gastrovegetalin; Lomaherpan; *Rus.*: Lomaherpan (Ломагерпан); Novo-Passit (Ново-Пассит); *Swed.*: Valerina; *Switz.*: Valverde Boutons de fievre creme.

Multi-ingredient Preparations. *Arg.*: Alcachofa Plus; Nervocalm; Sabelin; Valeriana Compuesta; Valeriana Oligoplex; Valeriana Relax Diates†; *Austral.*: Executive Sleep Formula; Herbal Rest & Relax; Natural Deep Sleep†; Nyal Night-Time Cough; Nyal Sleep Aid; Sleep Sound Formula; *Austria*: Abdomilon N; Baldracin; Baldrian comp; Iberogast; Klosterfrau Melissengeist; Mariazeller; Passedan; Sedogelat; The Chambard-Tee; Wechseltee St Severin; *Belg.*: Calmiplant; Eau Des Carmes; Minhavez; Songha†; *Braz.*: Balsamo Branco; Bronquiogen†; Calmapax; Camomila; Passaneuro; Sedantol; Sonhare; *Canad.*: Bilonat; Detente†; Dormane Plus; Formula T4†; Natural HRT Nightime; Relaxant; Relaxol; Salusan†; Swiss Herb Cough Drops; *Chile*: Bebe Son; Melipass; Perfect Body; Recalm†; *Cz.*: Alvisan Neo; Baldracin†; Euvekan†; Fytokliman Planta; Hypotonicka†; Iberogast; Klosterfrau Melisana; Nervova Cajova Smes; Novo-Passit; Passedan†; Passit; Persen; Species Nervinae Planta; Valofyt Neo†; *Denm.*: Relana†; *Fr.*: Aromazen†; Azema†; Biocarde; Boribel Tisane No 6†; Calmotisan†; DNV; Dystolise; Elixir Bonjean†; Herpclair; Mediflor Circulation du Sang No 12†; Mediflor Pectorale d'Alsace no 8†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Omezelis; Phytozac; Phytozac; Santane C_4†; Santane D_3†; Santane N_6; Vagostabyl; *Ger.*: Abdomilon N; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Euvegal Entspannungs- und Einschlaftropfen; Euvegal; Heumann Beruhigungstee Tenerval; Iberogast; Klosterfrau Melissengeist; Melissengeist; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival forte; Plantival novo; Sandrin; Seda-Plantina N; Sedacur; Sedariston plus†; Valeriana Beruhigungsdragees; Vivinox Day; *Hung.*: Antifront; Antifront; Antipoll; Carmol; Crategil; Euvekan†; Herbalakt; Herpesil; Iberogast; Klosterfrau Melisana; Menofit; Mensesyl; Sedacur; Sedogelat; Telma; Travelon; Worishofener; *Israel*: Songha Night; *Ital.*: Actenacol; Calmason; Colimil; Dormiplant; Emmenoiasi; Enatus; Ginepausil; Lenifren; Sedatol; Tisana Kelemata; Vagostabil Junior; Vagostabil; *Malaysia*: Circarol; *Mex.*: Nordimenty; Plantival; *Neth.*: Iberogast; *Norw.*: Euvekan†; Sobal†; Songha Natt; Valerina Natt; *NZ*: Botanica Hayfever; Mr Nits; *Philipp.*: Circulan; *Pol.*: Amarosal; Aromatol; Bobofen†; Calmina; Carmolis; Cravisol; DexaCaps; Doppelherz Energovital Tonik K; Dormiplant; Iberogast; Klimax; Lumewal; Melisal; Melisana Klosterfrau; Melissed; Nervinolum; Nervinum†; Nervomag; Nervomix; Nervosan†; Nervosol; Nerwobonisol; Perfocrat†; Persen; Psychotonisol†; Relana†; Sedomix; Somnoten†; Tabletki Uspokajajace; Ulventroten†; *Rus.*: Cedoflor (Седофлор); Doppelherz Melissa (Доппельгерц Мелисса); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Dormiplant (Дормиплант); Persen (Персен); Phyto Novo-Sed (Фито Ново-Сед); *S.Afr.*: Melissengeist†; Spiritus Contra Tussim Drops†; *Singapore*: Stop Snoring; *Spain*: Agua del Carmen; Dormiplant†; Iberogast; Melival; Nervikan; Relana†; Resolutivo Regium†; Solucion Schoum; *Swed.*: Iberogast; Sedacur; *Switz.*: Arterosan Plus†; Baldriparan; Cardiaforce; Dormiplant; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Femisan; Gastrosan; Hyperiforce comp; Iberogast; Kernosan 26; Metabol; Relaxane; Relaxo; Songha Night; Tisane calmante pour les enfants; Tisane favorisant l'allaitement; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs; Tisane pour nourissons et enfants; Valverde Detente dragees; *Turk.*: Nervikan; Nevrol Cemal; *UK*: DiaDay & Night; DiaRelax; Digestion Calming Drops; Melissa Comp.; Puncto SleepTight; Spotner; Valerina Day Time; Valerina Night-Time; *Ukr.*: Antifront (Антифронт); Antifront (Антифронт); Dormiplant (Дормиплант); Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Iberogast (Иберогаст); Klimased (Климасед); Normoton (Нормотон); Novo-Passit (Ново-Пассит); Persen (Персен); Relaxil (Релаксил); Sedasen (Седасен); *Venez.*: Euvekan; Sedival.

Homoeopathic Preparations. *Austria*: Valerianaheel; *Canad.*: Lemon Balm†; Motherwort Combination 3†; Valerianaheel Comp†; *Chile*: Melinerv; *Ger.*: Myonasan; Roth's RKT Tropfen; *Neth.*: Neurovita; *UK*: Cough Drops.

Melissa Oil

Balm Oil; Esencia de Melisa; Lemon Balm Oil; Мелиссовое Масло.

CAS — 8014-71-9.

ATC Herb — HN05CM5014 (Melissa officinalis: essential oil).

UNII — MJ76269K9S.

Profile

Melissa oil is the essential oil obtained from melissa (*Melissa officinalis*), p. 2552.3. It is used in preparations with other essential oils in a variety of disorders. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Opino; *Canad.*: Melisana†; *Chile*: Agua del Carmen; Agua Melisa Carminativa; *Cz.*: Thrombocid; *Fr.*: Stomargil; *Ger.*: Amol Heilkrautergeist N; Thrombocid; *Gr.*: Opino; *Hung.*: Amol; Pasta Cool; *Indon.*: Opino†; *Ital.*: Altadrine Firming†; Dentosan Azione Intensiva; Dentosan Mese; Neuralta Migren; *Pol.*: Amol; Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Doppelherz Energovital Tonik†; *Port.*: Thrombocid; *Rus.*: Doppelherz Energotonik (Доппельгерц Энергетоник); *Switz.*: DUL-X warm; DUL-X.

Menbutone *(BAN, rINN)*

Menbuton; Menbutona; Menbutoni; Menbutonum; SC-1749 (menbutone sodium); Менбутон.

4-(4-Methoxy-1-naphthyl)-4-oxobutyric acid.

$C_{15}H_{14}O_4$=258.3

CAS — 3562-99-0.

ATC Vet — QA05AX90.

UNII — 341YM32546.

Profile

Menbutone is used as a choleretic to stimulate gastrointestinal function in veterinary medicine.

Menfegol *(rINN)*

Menfégol; Menfegolum; Menphegol; Менфеголум.

α-[p-(p-Menthyl)phenyl]-ω-hydroxypoly(oxyethylene).

$C_{16}H_{23}(OCH_2CH_2)_nOH$

CAS — 57821-32-6.

Profile

Menfegol is a macrogol aryl ether nonionic surfactant (p. 2164.2). It is used as a spermicide.

Adverse effects. Frequent use of menfegol in spermicidal foaming tablets has been associated with a high incidence of genital ulceration, which could increase the risk of infection by HIV.[1]

1. Goeman J, *et al.* Frequent use of menfegol spermicidal vaginal foaming tablets associated with a high incidence of genital lesions. *J Infect Dis* 1995; 171: 1611–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Neo Sampoon†; *Malaysia*: Neo Sampoon; *Philipp.*: Neo Sampoon; *Singapore*: Neo Sampoon†.

Menthol

Hexahydrothymol; Mentholum; Mentol; Mentoli; Mentolis; Ментол.

p-Menthan-3-ol; 2-Isopropyl-5-methylcyclohexanol.

$C_{10}H_{20}O$=156.3

CAS — 1490-04-6 (menthol); 15356-60-2 ((+)-menthol); 2216-51-5 ((-)-menthol); 89-78-1((±)-menthol).

UNII — L7T10EIP3A.

Description. Menthol is either the laevo-isomer, levomenthol (*BAN, rINN*), or a racemic mixture, racementhol (*BAN, rINN*). The laevo-isomer may be obtained from the volatile oils of various species of *Mentha* (Labiatae) or it may be prepared synthetically.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn, US*, and *Viet. Eur.* and *Jpn* have separate monographs for laevo-menthol (levomenthol) and racemic menthol (racementhol).

Ph. Eur. 8: (Levomenthol). It occurs as colourless, acicular or prismatic shiny crystals. M.p. about 43 degrees. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

Ph. Eur. 8: (Menthol, Racemic; Racementhol BP 2014). It occurs as colourless, acicular or prismatic shiny crystals or as a free-flowing or agglomerated crystalline powder. M.p. about 34 degrees. Practically insoluble in water; very soluble in alcohol and in petroleum spirit; freely soluble in fatty oils and in liquid paraffin; very slightly soluble in glycerol.

USP 36: (Menthol). An alcohol obtained from diverse mint oils or prepared synthetically. It may be laevorotatory (*l*-menthol), from natural or synthetic sources, or racemic (*dl*-menthol). It occurs as colourless, hexagonal crystals, usually needle-like, or in fused masses, or crystalline powder. Has a pleasant, peppermint-like odour. M.p. of *l*-menthol 41 degrees to 44 degrees. Slightly soluble in water; very soluble in alcohol, in chloroform, in ether, and in petroleum spirit; freely soluble in glacial acetic acid, in fixed and volatile oils, and in liquid paraffin. Store in airtight containers preferably at a temperature of 15 degrees to 30 degrees.

Compounding. A liquid or soft mass is formed when menthol is triturated with camphor, cloral hydrate, phenol, and many other substances.

Methods of preparing menthol 1% w/w in aqueous cream BP and the stability of the resultant product have been discussed.[1]

1. Cable C. The preparation of menthol (1 per cent w/w) in aqueous cream BP. *Pharm J* 2005; 274: 469.

Uses and Administration

Menthol is chiefly used to relieve symptoms of bronchitis, sinusitis, and similar conditions. For this purpose it may be used as an inhalation, usually with benzoin or eucalyptus oil, as pastilles, or as an ointment with camphor and eucalyptus oil for application to the chest or nostrils (but see Adverse Effects below). However, as mentioned under the section on the management of cough (p. 1651.2), the use of menthol in inhalations is unlikely to provide any additional benefit.

When applied to the skin menthol dilates the blood vessels, causing a sensation of coldness followed by an analgesic effect. It relieves itching and is used in creams, lotions, or ointments in pruritus and urticaria. It has also been applied to the forehead, presumably as a counter-irritant, for the relief of headache.

In small oral doses menthol has a carminative action.

A review[1] of menthol's actions and uses noted that menthol elicited a cool sensation by acting on the TRPM8 receptor, a thermosensitive cation channel that is also activated by low temperature.

1. Patel T, *et al.* Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol* 2007; 57: 873–8.

Neuropathic pain. Topical application of 0.5% menthol in calamine cream twice daily has been reported to relieve severe neuropathic pain induced by bortezomib in a 69-year-old man.[1]

1. Colvin LA, *et al.* From bench to bedside: a case of rapid reversal of bortezomib-induced neuropathic pain by the TRPM8 activator, menthol. *J Clin Oncol* 2008; 26: 4519–20.

Adverse Effects, Treatment, and Precautions

Menthol may give rise to hypersensitivity reactions including contact dermatitis. Ingestion of significant quantities of menthol is reported to cause symptoms similar to those seen after ingestion of camphor (p. 2466.3), including severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma; they may be managed similarly. There have been reports (below) of apnoea and instant collapse in infants after the local application of menthol to their nostrils.

Administration to infants. Instillation of decongestant preparations containing menthol directly into the nostrils of infants and young children has resulted in acute respiratory distress with cyanosis[1] and respiratory arrest,[2] and must be avoided. In one case,[1] nasal application was associated with concurrent chemical conjunctivitis.

1. Wyllie JP, Alexander FW. Nasal instillation of 'Olbas Oil' in an infant. *Arch Dis Child* 1994; 70: 357–8.
2. Blake KD. Dangers of common cold treatments in children. *Lancet* 1993; 341: 640.

Effects on the nervous system. A 13-year-old boy developed ataxia, confusion, euphoria, nystagmus, and diplopia after inhaling 5 mL of Olbas oil instead of the recommended few drops.[1] It was considered probable that the menthol in the preparation was responsible for the symptoms; the amount of menthol inhaled was about 200 mg.

1. O'Mullane NM, *et al.* Adverse CNS effects of menthol-containing Olbas oil. *Lancet* 1982; i: 1121.

Pharmacokinetics

After absorption, menthol is excreted in the urine and bile as a glucuronide.

Absorption. The systemic absorption of camphor, menthol, and methyl salicylate from dermal patches containing all three ingredients has been studied.[1] The absolute bioavailability of these compounds could not be determined from this study, but there did not appear to be any substantial systemic accumulation even after unrealistically high exposure for prolonged periods.

1. Martin D, *et al.* Dermal absorption of camphor, menthol, and methyl salicylate in humans. *J Clin Pharmacol* 2004; **44**: 1151–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flex-All; Rati Salil Ice; *Austral.*: Dencorub Arthritis Ice; Ice Gel; Vicks Vapodrops Butter and Menthol†; *Canad.*: Absorbine Jr Roll-on Ice†; Absorbine Jr; Absorbine Power Gel; Artic Ice†; Blue Ice Rub; Certified Ice†; Cough Lozenges; Deep Cold; Everflex; Formula G9†; Formula TT†; Formula TTO†; Gel Glace†; Glenalgesic Blue†; Ice Gel Therapy; Medicated Foot Powder†; Polar Ice†; Rub A-535 Antiphlogistine Ice; Soothing Ice Rub†; Vicks VapoDrops; *Chile*: Friorub; Hielorub†; Mentholatum Patch; *Hong Kong*: Bengay Patch; Counterpain†; *Hung.*: Salonpas Gel-Patch; *India*: Capsigyl-D; Dolocide Plus; Icegel; *Indon.*: Blue Cap; Counterpain Cool; *Irl.*: Deep Freeze Cold Gel; Meggezones; *Jpn*: Minclea; *Malaysia*: Menzza Ice; *NZ*: Vicks Throat Drops; Vicks Vapodrops; *Pol.*: Migrenol†; *Port.*: Vicks Vaporub; *Singapore*: Bengay Patch; Bengay Vanishing; Counterpain Cool; *Spain*: Prulit†; *Switz.*: Perskindol Cool; *Thai.*: Centropain; Counterpain Cool; Painza Cool; Stopain; *UK*: 4Head; Arjun Cream; Benylin Mucus Cough Menthol; Deep Freeze Cold Gel; Dermacool; Happinose; Ice Cool Stress & Tension Relief; Meggezones; Quool; Vicks Cough Syrup with Honey for Dry & Irritating Coughs; Vicks Vaposyrup for Tickly Coughs; *USA*: Absorbine Jr; Ben-Gay Patch; Ben-Gay Vanishing; Biofreeze; Cepacol Regular Strength; Cepacol Sore Throat Post Nasal Drip; Cold & Hot Pain Relief Therapy Patch; Extra Strength Vicks Cough Drops; Halls-Plus Maximum Strength; Icy Hot Back Pain Relief; Icy Hot Pain Relieving; Icy Hot PM; Icy Hot Pop & Peel; Icy Hot Pro-Therapy; Icy Hot Roll; Kof-Eze; Mineral Freez Gel; N'ice 'n Clear; N'ice; Ricola Herb; Salonpas Aqua Patch†; Sportscreme Ice; Stopain Cold; Therapeutic Mineral Ice; Therapy Ice; Vicks Cough Drops; Wonder Ice; *Venez.*: Dencorub Ice.

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

Homoeopathic Preparations. *Austria*: Exanginа†; *Ger.*: Mullersche Tabletten.

Pharmacopoeial Preparations
BP 2014: Levomenthol Cream; Menthol and Benzoin Inhalation; USP 36: Benzocaine and Menthol Topical Aerosol; Menthol Lozenges; Tetracaine and Menthol Ointment.

Menthol Esters

Menthyl Esters.

Menthyl acetate

Menthol Acetate; Mentylu octan.
5-Methyl-2-(1-methylethyl)cyclohexyl acetate.
$C_{12}H_{22}O_2$=198.3
CAS — 89-48-5; 16409-45-3.
UNII — W8CSF4H1OA.

Menthyl Isovalerate

Menthol Isovalerate; Menthyl Valerate.
5-Methyl-2-(1-methylethyl)cyclohexyl 3-methylbutanoate.
$C_{15}H_{28}O_2$=240.4
CAS — 28221-20-7; 89-47-4; 16409-46-4.
UNII — E6QE751102.

NOTE. The name Validol has been used both as a synonym for menthyl isovalerate and as a proprietary name for a preparation containing it.

Menthyl Lactate

Menthol Lactate; *l*-Menthyl Lactate.
5-Methyl-2-(1-methylethyl)cyclohexyl 2-hydroxypropanoate.
$C_{13}H_{24}O_3$=228.3
CAS — 59259-38-0.
UNII — 2BF9E65L7I.

Profile

Esters of menthol such as the acetate, isovalerate, and lactate are readily hydrolysed to menthol (p. 2553.2) and have similar properties. They are used as flavourings and perfumes, and for their cooling properties in skin-care products.

Menthyl isovalerate also shares some properties with isovaleric acid (p. 2641.2) and has been used similarly. Preparations containing what has been variously described as menthyl isovalerate or a solution of menthol in menthyl isovalerate have been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Darvalidol†; Mentowal; Validol; *Rus.*: Validol (Валидол); *Ukr.*: Corvalment (Корвальмент); Validol (Валидол).

Multi-ingredient Preparations. *Belg.*: Purigel Crisp†; Purigel NF; *Hung.*: Nicobrevin; *Irl.*: Nicobrevin†; *Ital.*: Blogofort†; Flogofort Cremagel; Pitiren; *NZ*: Nicobrevin; *Rus.*: Barboval (Барбовал); Carniland (Карниланд); *UK*: Nicobrevin; *Ukr.*: Barboval (Барбовал).

Menthone

(*dl*)-menthone; Menton; Ментон; (±)-menthone.
(2*R*,5*S*)-*rel*-5-Methyl-2-(1-methylethyl)cyclohexanone.
$C_{10}H_{18}O$=154.3
CAS — 3391-87-5 ((+)-menthone); 14073-97-3 ((-)-menthone); 89-80-5 ((±)-menthone); 1196-31-2 ((+)-isomenthone); 491-07-6 ((±)-isomenthone).

Profile

Menthone is a constituent of several essential oils. Of the 4 possible stereoisomers of menthone, (-)-menthone (*l*-menthone) is the most abundant in nature. Menthone is reported to be a cholagogue and has been used in preparations for biliary-tract and liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Rowachol; *Cz.*: Rowachol; *Ger.*: Rowachol; *Hong Kong*: Neo-Rowachol; Rowachol; *Hung.*: Rowachol; *Irl.*: Rowachol; *Israel*: Rowachol; *Malaysia*: Rowachol; *Mex.*: Cholex; *Philipp.*: Rowachol; *Pol.*: Rowachol; Terpichol; *Thai.*: Rowachol; *UK*: Rowachol; *Venez.*: Rowachol.

Menyanthes

Bitterklee; Bogbean; Buckbean; Folia Trifoli Fibrini; Liść bobrka (bogbean leaf); Marsh Trefoil; Ményanthe; Menyanthidis Folium (bogbean leaf); Menyanthidis trifoliatae folium; Raatteenlehti (bogbean leaf); Trébol acuático; Trébol de agua; Trébol fabrino; Trèfle d'Eau; Trifolii Fibrini Folium (bogbean leaf); Trilapių pupalaiškių lapai (bogbean leaf); Vachtový list (bogbean leaf); Vattenklöverblad (bogbean leaf); Vidrafűlevél (bogbean leaf); Вахта Трёхлистная.
ATC Herb — HA09WA5019 (Menyanthes trifoliata leaf).
UNII — 7H0QTZ446K (Menyanthes trifoliata); GYG64DIH9P (Menyanthes trifoliata leaf); 38S191W4O2 (Menyanthes trifoliata root).

NOTE. Bog myrtle (see p. 2458.3) has also been used as a common name for *Menyanthes trifoliata*.

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

Ph. Eur. 8: (Bogbean Leaf). The dried, entire or fragmented leaf of *Menyanthes trifoliata*. It has a very bitter and persistent taste.

Profile

Menyanthes has been used as a bitter. It is used in herbal medicine for rheumatic, gastrointestinal, and biliary-tract disorders. It is also used in folk medicine.

Homoeopathy

Menyanthes has been used in homoeopathic medicines under the following names: Menyanthes trifoliata; Menyanthes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Mariazeller; Pervivo; *Canad.*: Gallexier†; *Fr.*: Tisane Hepatique de Hoerdt†; *Ger.*: Gallexier; *Hung.*: Bittner; *Pol.*: Krople Zoladkowe†; Krople Zoladkowe; Pervivo; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *UK*: Modern Herbals Rheumatic Pain; Rheumatic Pain Relief; Rheumatic Pain Remedy; Rheumatic Pain; Vegetex; *Ukr.*: Trivalumen (Тривалумен).

Homoeopathic Preparations. *Austral.*: Echine†; *Canad.*: Alfalfa Tonic; *Fr.*: Cereales Germees.

Mercaptamine *(BAN, rINN)*

Cysteamine (USAN); Cysteamine; L-1573; MEA; Mercamine; Mercaptamina; Mercaptaminum; Merkaptamiini; Merkaptamin; Меркаптамин.
2-Aminoethanethiol.
C_2H_7NS=77.14
CAS — 60-23-1.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — 5UX2SD1KE2.

NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine (p. 820.3) and mercaptamine (formerly cysteamine) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Mercaptamine Bitartrate *(BANM, rINNM)*

Bitartrato de mercaptamina; Cysteamine Bitartrate; Mercaptamina, bitartrato de; Mercaptamine, Bitartrate de; Mercaptamini Bitartras; Меркаптамина битартрат.
$C_2H_7NS, C_4H_6O_6$=227.2
CAS — 27761-19-9.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — QO84GZ3T5T.

Mercaptamine Hydrochloride *(BANM, rINNM)*

CI-9148; Cysteamine Hydrochloride (USAN); Hidrocloruro de mercaptamina; Mercaptamina, hidrocloruro de; Mercaptamine, Chlorhydrate de; Mercaptamini Hydrochloridum; Меркаптамина Гидрохлорид.
C_2H_7NS,HCl=113.6
CAS — 156-57-0.
ATC — A16AA04.
ATC Vet — QA16AA04.
UNII — IF1B771SVB.

Uses and Administration

Mercaptamine reduces intracellular cystine levels and is given orally as the bitartrate and as eye drops containing the hydrochloride in the treatment of cystinosis (see p. 2555.1). Doses are expressed in terms of the base: 2.94 g of the bitartrate or 1.47 g of the hydrochloride are each equivalent to 1 g of mercaptamine.

In the treatment of nephropathic cystinosis, mercaptamine bitartrate is given in an initial dose that is one-sixth to one-quarter of the expected maintenance dose, and is then increased gradually over 4 to 6 weeks. The usual maintenance dose in patients over 12 years of age and weighing over 50 kg is 2 g daily of the base in divided doses. Daily doses above 1.95 g/m² are not recommended. Immediate-release preparations are given in 4 divided doses with or after food and modified-release preparations are given twice daily at least 2 hours after or 30 minutes before eating. Doses are given in conjunction with monitoring of leucocyte-cystine levels, which should be kept below 1 nanomol of hemicystine per mg of protein. Doses for children under 12 years of age or weighing under 50 kg are given below.

Phosphocysteamine, a phosphorothioester of mercaptamine, has been said to be more palatable, and has been used similarly.

Mercaptamine is also used in the treatment of corneal cystine crystal deposits in patients with cystinosis. It is administered as eye drops containing mercaptamine hydrochloride 6.5 mg/mL (equivalent to mercaptamine 0.44%); one drop is instilled into each eye every hour. Eye drops containing mercaptamine 0.11% or 0.55% have also been used.

Mercaptamine is under investigation for the treatment of Huntington's disease and nonalcoholic fatty liver disease in children.

Administration in children. Doses of mercaptamine for the treatment of cystinosis in children should be calculated on the basis of body-surface because of a risk of Ehlers-Danlos-like syndrome with high doses (see Adverse Effects p. 2555.1). The recommended maintenance dose of mercaptamine given orally to children up to 12 years of age or weighing under 50 kg is 1.3 g/m²(about 50 mg/kg) daily in divided doses. Doses should be reduced if any skin or bone abnormalities appear. Daily doses above 1.95 g/m² are not recommended. Lower starting doses and monitoring of leucocyte-cystine levels are recommended as described under Uses and Administration, above.

For children at risk of aspiration or who have difficulty swallowing, the contents of immediate-release capsules may be sprinkled on food, although not in acidic drinks.

Similarly, the contents of modified-release capsules may be mixed with a small amount of liquid or soft food, for example orange juice or apple sauce.

Cystinosis. Mercaptamine is used in the treatment of cystinosis, a rare autosomal recessive metabolic disorder characterised by the intracellular accumulation of cystine. Cystinosis is marked by growth retardation, rickets, Fanconi syndrome, and renal failure necessitating transplantation; acute episodes of acidosis and dehydration may occur. Hypothyroidism generally develops and puberty is delayed in males.[1,2] Photophobia and loss of visual acuity are associated with deposition of cystine in the eye.[3]

Oral mercaptamine treatment is given to increase cystine clearance from cells. It can delay the development of end-stage renal disease, reduce the incidence of extrarenal complications,[4-7] and improve life expectancy.[5,7] Treatment is most effective when started early, at the time of diagnosis in infancy or early childhood.[7,8]

Mercaptamine eye drops are used to dissolve corneal cystine crystals because oral therapy is ineffective.[9] Treatment must be applied frequently throughout the day; photophobia may be relieved within weeks[2] and crystals dissolved over several months.[1]

1. Wilmer MJ, *et al.* Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol* 2011; **26:** 205–15.
2. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol* 2013; **28:** 51–9.
3. Dureau P, *et al.* Evolution of ocular manifestations in nephropathic cystinosis: a long-term study of a population treated with cysteamine. *J Pediatr Ophthalmol Strabismus* 2003; **40:** 142–6.
4. Gahl WA, *et al.* Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987; **316:** 971–7.
5. Gahl WA, *et al.* Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* 2007; **147:** 242–50.
6. Greco M, *et al.* Long-term outcome of nephropathic cystinosis: a 20-year single-center experience. *Pediatr Nephrol* 2010; **25:** 2459–67.
7. Brodin-Sartorius A, *et al.* Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int* 2012; **81:** 179–89.
8. Markello TC, *et al.* Improved renal function in children with cystinosis treated with cysteamine. *N Engl J Med* 1993; **328:** 1157–62.
9. Kaiser-Kupfer MI, *et al.* A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990; **108:** 689–93.

Adverse Effects and Precautions

Mercaptamine can be unpalatable and may cause breath and body odour. It may cause gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain, and occasionally, gastrointestinal ulceration. Other adverse effects may include drowsiness, lethargy, headache, rashes, fever, and encephalopathy. Mercaptamine may cause leucopenia, increases in liver enzyme values, and nephrotic syndrome. Nervousness, hallucinations, and benign intracranial hypertensionhave also been reported. A few cases of Ehlers-Danlos-like syndrome (a connective tissue disorder) affecting the elbows have been reported in children treated with high doses of mercaptamine. Skin should be monitored regularly and bones examined by X-ray as necessary; the patient and their parents should also be advised to examine the skin regularly. Recommended doses should not be exceeded—see Administration in Children, p. 2554.3.

The most common adverse effects reported with mercaptamine eye drops are sensitivity to light, eye pain and irritation, visual field defects, and headache.

Mercaptamine is contra-indicated in patients with penicillamine hypersensitivity.

Intolerance. Three patients with nephropathic cystinosis developed fever, maculopapular eruption, leucopenia, or headache within 2 weeks of starting oral mercaptamine at doses of 53, 67, and 75 mg/kg daily, respectively.[1] These adverse effects resolved within 48 hours of drug withdrawal and all 3 patients were able to tolerate mercaptamine when restarted at a dose of 10 mg/kg daily, slowly increased to therapeutic levels over 2 to 3 months. Higher doses of mercaptamine had been associated with lethargy and seizures.

1. Schneider JA, *et al.* Cysteamine therapy in nephropathic cystinosis. *N Engl J Med* 1981; **304:** 1172.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mercaptamine 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 06/10/11)

Pharmacokinetics

Mercaptamine is absorbed from the gastrointestinal tract, and the peak plasma concentration is reached in about 1.4 hours. It is about 54% bound to plasma proteins, mainly albumin. Mercaptamine has a terminal elimination half-life of about 4.8 hours, and most of a dose is excreted as the sulfate.

Children. Results of a pharmacokinetic-pharmacodynamic study[1] in paediatric patients with nephropathic cystinosis showed that although mercaptamine is rapidly cleared from plasma, dosing every 6 hours was sufficient to maintain the content of cystine in the white blood cells below the target value (see p. 2554.3).

1. Belldina EB, *et al.* Steady-state pharmacokinetics and pharmacodynamics of cysteamine bitartrate in paediatric nephropathic cystinosis patients. *Br J Clin Pharmacol* 2003; **56:** 520–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cystagon; *Austria*: Cystagon; *Belg.*: Cystagon†; *Cz.*: Cystagon; *Denm.*: Cystagon; *Fin.*: Cystagon; *Fr.*: Cystagon; *Ger.*: Cystagon; *Irl.*: Cystagon; *Ital.*: Cystagon; *Neth.*: Cystagon; *Norw.*: Cystagon; *Pol.*: Cystagon; *Port.*: Cystagon; *Spain*: Cystagon; *Swed.*: Cystagon; *UK*: Cystagon; *USA*: Cystagon; Cystaran; Procysbi.

Mercuric Chloride

Bicloruro de Mercurio; Chlorid rtutnaty; Cloreto Mercúrico; Corrosive Sublimate; Gyvsidabrio dichloridas; Higany(II)-klorid; Hydrarg. Perchlor.; Hydrargyri Dichloridum; Hydrargyri Perchloridum; Hydrargyrum Bichloratum; Kvicksilverdiklorid; Mercuric Chlor.; Mercúrico, cloruro; Mercurique (Chlorure); Mercurique, chlorure; Mercury Bichloride; Mercury Perchloride; Merkuridikloridi; Quecksilberchlorid; Quecksilber(II)-chlorid; Rtęci(II) chlorek.

$HgCl_2$=271.5

CAS — 7487-94-7.

ATC — D08AK03.

ATC Vet — QD08AK03.

UNII — 53GH7MZT1R.

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

Ph. Eur. 8: (Mercuric Chloride). A white or almost white, crystalline powder, or colourless or white or almost white crystals or heavy crystalline masses. Soluble in water and in glycerol; freely soluble in alcohol. Protect from light.

Profile

The use of mercuric chloride as an antibacterial substance is limited by its toxicity, its precipitating action on proteins, its irritant action on raw surfaces, its corrosive action on metals, and by the fact that its activity is greatly reduced in the presence of excreta or body fluids.

Details of the adverse effects of inorganic mercury compounds are provided under Mercury, p. 2556.1.

Homoeopathy

Mercuric chloride has been used in homoeopathic medicines under the following names: Chlorure mercurique; Corrosive sublimate; Hydrargyri bichloridum; Mercurius corrosivus; Quecksilberchlorid; Sublimé corrosif.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Neth.*: Diarrheel S.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Canad.*: Detox L37; PMS; *Fr.*: Abbe Chaupitre no 18†; Agnus Castus Complexe No 2†; Angipax; Cimicifuga Complexe No 21†; Cina Complexe No 55†; Cistus Canadensis Complexe No 86†; Echinacea Complexe No 40; Geranium Complexe No 108†; Hedera Complexe No 120; Iodum Complexe No 118; Juniperus Complexe No 6; Kalium Muriaticum Complexe No 41†; L 107; Pareira Brava Compose; Pulsatilla Complexe No 60†; Rhus Toxicodendron Complexe No 80; Symphytum Complexe No 48†; Thuya Complexe No 37; Urarthone; Urtica Complexe No 82†; *Ger.*: Angina-Gastreu S R1; Entero-Gastreu S R4; Hewesoor N†; Kinolymphat†; Pascorenal-Injektopas; Phonix Silybum spag; Phonix Solidago spag; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; *Neth.*: Belachin-Gastreu R1; Entero-Gastreu R4; Phonix Hydrargyrum; Phonix Solidago comp; *Switz.*: Diarrheel S.

Yellow Mercuric Oxide

Gelbes Quecksilberoxyd; Hydrargyri Oxidum Flavum; Hydrargyri Oxydum Flavum; Mercúrico amarillo, óxido; Mercurique (Oxyde) Jaune; Oxido Amarillo de Mercurio; Óxido de mercurio amarillo; Yellow Precipitate; Жёлтая Окись Ртути.

HgO=216.6

CAS — 21908-53-2.

Pharmacopoeias. In *Fr.* and *It.*

Profile

Yellow mercuric oxide has been used in eye ointments for the local treatment of minor infections including the eradication of pubic lice from the eyelashes. Absorption can occur and produce the adverse effects of inorganic mercury (see Mercury, p. 2556.1).

Pediculosis. Yellow mercuric oxide 1% eye ointment was considered to be a safe and effective treatment in pediculosis (p. 2147.3) of the eyelashes caused by pubic lice (pthiriasis palpebrarum).[1]

1. Ashkenazi I, *et al.* Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum. *Br J Ophthalmol* 1991; **75:** 356–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Pomada Amarilla; *Fr.*: Ophtergine; Pommade Maurice†.

Multi-ingredient Preparations. *India*: Bell Diono Resolvent†; Bell Resolvent†.

Mercurous Chloride

Quecksilberchlorür; Calomel; Calomelanos; Cloreto Mercuroso; Hydrarg. Subchlor.; Hydrargyri Subchloridum; Hydrargyrosi Chloridum; Hydrargyrum Chloratum (Mite); Mercureux (Chlorure); Mercurioso, cloruro; Mercurius Dulcis; Mercury Monochloride; Mercury Subchloride; Mild Mercurous Chloride; Monocloruro de mercurio; Protocloruro de Mercurio.

HgCl = 236.0; Hg_2Cl_2 = 472.1

CAS — 7546-30-7 (HgCl); 10112-91-1 (Hg_2Cl_2).

UNII — J2D46N657D.

NOTE. Precipitated Mercurous Chloride (Hydrargyri Subchloridum Praecipitatum), is a white amorphous powder, for which the synonym 'White Precipitate' (Praecipitatum Album) has been used. White Precipitate has also been used as a name for Ammoniated Mercury.

Pharmacopoeias. In *Chin.* as Hg_2Cl_2.

Profile

Mercurous chloride was formerly given as a laxative and was applied topically as an antibacterial. It was one of the mercury compounds used in the management of syphilis in the pre-antibiotic era.

The mercurous form of mercury does not possess the corrosive properties of the mercuric form and is not absorbed to any great extent. However, the mercurous form can be converted to the mercuric, with consequent toxicity as described under Mercury (see p. 2556.1).

Homoeopathy

Mercurous chloride has been used in homoeopathic medicines under the following names: Mercurius dulcis; Merc dulc.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Abbe Chaupitre no 88†; Aconitum Compose†; Allium Cepa Compose; Hepatocynesine†; Scrofularia Compose; *Neth.*: Oteel H; *Switz.*: Alceprin-N.

Mercury

Azogue; Hidrargirio; Hydrarg.; Hydrargyrum; Hydrargyrum Depuratum; Mercure; Mercurio; Quecksilber; Quicksilver; Rtęć; Ртуть.

Hg=200.592

CAS — 7439-97-6.

ATC — D08AK05.

UNII — FXS1BY2PGL (mercury); ED30FJ8Y42 (mercuric ion).

Description. Mercury is a shining, silvery white, very mobile liquid, easily divisible into globules, which readily volatilises on heating.

Uses

The hazards associated with mercury generally outweigh any therapeutic benefit and its clinical use has largely been abandoned. The use of mercurial diuretics such as mersalyl has generally been superseded by other diuretics. Ointments containing mercurials, such as ammoniated mercury (p. 1711.3) have also generally been replaced by less toxic preparations. Mercurials were formerly used as spermicides.

Some ionisable inorganic mercury salts and certain organic compounds of mercury have been used as disinfectants, and some mercury salts are effective parasiticides and fungicides. Organic mercurials such as phenylmercuric acetate, borate, and nitrate are also used as preservatives (p. 1765.1). Mercury is a component of dental amalgams.

Other mercury salts that have been used for their antibacterial activity include mercuric chloride, yellow mercuric oxide, mercurous chloride (above), and thiomersal (p. 1771.3).

Homoeopathy

Mercury and some mercury compounds have been used in homoeopathic medicines. The precise identity of the substances is not always clear but the following names have been used:

- Mercury: Hydrargyrum metallicum; Mercurius vivus; Merc. viv.
- Mercuric cyanide: Hydrargyrum bicyanatum; Mercurius cyanatus; Merc cyan
- Mercuric iodide: Mercurius iodatus flavus; Merc iod flav; Merc. i. f.
- Red mercuric iodide: Hydrargyrum biiodatum; Mercurius bijodatus; Mercurius iodatus ruber;Merc iod rub; Merc. i. r.
- Mercurous nitrate: Hydrargyrum nitricum oxydulatum; Mercurius nitricus oxydulatus; Mercurius nitricus; Merc. nit.
- Red mercuric sulfide: Hydrargyrum sulfuratum rubrum; Cinnabaris; Cinbar.
- Ammoniated mercuric nitrate: Mercurius solubilis; Merc. sol.
- Potassium mercuric iodide: Mercurius et kali iodatus; Merc. ki.
- Red mercuric oxide: Hydrargyri Oxidum Rubrum; Red Precipitate; Oxyde Rouge de Mercure; Mercurius Praecipitatus Ruber
- Mercuric sulfate: Mercurius sulphuricus; Hydrargyrum sulfuricum; Mercurius sulfuricus; Hydrargyricus sulfas

See also Ammoniated Mercury (p. 1711.2), Mercuric Chloride (p. 2555.2), and Mercurous Chloride (p. 2555.3).

Adverse Effects

Poisoning with liquid mercury or inorganic mercury salts has arisen from sources such as batteries, cosmetics, dental materials, medical equipment, and jewellery manufacture. Barometers, sphygmomanometers, and thermometers are still sources of liquid mercury. Trace amounts of organic and inorganic mercury may also be ingested in the diet.

The effects of **acute** exposure depend on the nature of the compound.

- *Elemental (liquid) mercury* if ingested is poorly absorbed and, unless there is aspiration or pre-existing gastrointestinal disorders, is not considered to be a severe toxicological hazard. The greatest dangers from elemental mercury arise from the inhalation of mercury vapour, which can cause gastrointestinal effects including nausea, vomiting, and diarrhoea; more importantly it is toxic to the respiratory system and this effect can be fatal. Some CNS involvement has also been reported. Adverse effects have also been reported after accidental or intentional parenteral dosage.
- *Inorganic salts* such as mercuric chloride are corrosive when ingested causing severe nausea, vomiting, pain, bloody diarrhoea, and necrosis. The kidney is also involved and tubular necrosis may develop. Mercurous salts are considered to be less hazardous, but the mercurous form can be converted to the mercuric.
- *Organic mercurial compounds* produce similar toxic effects to inorganic compounds, but they have a more selective action on the CNS that has proved difficult to treat. The degree of toxicity varies; those used as preservatives or disinfectants are less toxic than the ethyl or methyl compounds that are not used pharmaceutically or clinically. Methylmercury is notorious for its toxicity; there have been cases of fetal neurotoxicity during outbreaks of methylmercury poisoning.

Chronic mercury poisoning may result from inhalation of mercury vapour, skin contact with mercury or mercury compounds, or ingestion of mercury salts over prolonged periods. It is characterised by many symptoms including tremor, motor and sensory disturbances, mental deterioration, gastrointestinal symptoms, dermatitis, kidney damage, salivation, and gingivitis. A blue line may be present on the gums. There is little difference between acute and chronic poisoning with organic mercurials.

The syndrome of *acrodynia* (pink disease), with symptoms of sweat, rash, erythema of the extremities, photophobia, wasting, weakness, hypertension, tachycardia, and diminished reflexes, occurred in children given mercury in teething powders or in ointments or dusting powders. Such preparations have long since been withdrawn from use. However, the syndrome is still a feature of mercury poisoning from other sources.

Hypersensitivity to mercury and mercurial compounds has been reported.

Mercurialentis has been reported in patients treated with eye drops containing an organomercurial preservative.

Chronic exposure. Acute *occupational exposure* to mercury vapour in 53 men resulted in an initial phase described as metal fume fever, an intermediate phase of severe symptoms with CNS, gastrointestinal, respiratory, and urological involvement, and a late phase with persistent CNS symptoms, dysuria, and pain on ejaculation.[1,2] Although persistent hyperchloraemia was noted in the 11 patients with the highest mercury levels, renal impairment tended to be temporary.[2]

Long-term follow-up of a patient who had an intravenous *injection* of mercury 12 years previously also revealed no persistent renal impairment,[3] despite the presence of mercury microemboli in lungs, kidneys, liver, and subcutaneous tissues and high concentrations in the urine. At this time, the patient had residual reductions in respiratory function, polyneuropathy, and marked asthenozoospermia. Spermatozoal abnormalities may also have contributed to his wife's miscarriage. Mercury deposits mimicking gallbladder cancer were found in the gallbladder of a patient 35 years after he had injected himself with elemental mercury.[4]

Fetal neurotoxicity after *maternal exposure* to methylmercury is well recognised, and there has been widespread concern about the effect of maternal diets on the developing fetus because of mercury concentrations in freshwater and marine organisms. Results from a study in the Faroe Islands showed an association between delays in neurological development in children and maternal consumption of pilot whale meat.[5] Follow-up studies of this population when they reached 14 years of age suggest that the neurotoxic effects of methylmercury might compromise brain development into the teenage years,[6] as well as affecting autonomic regulation of heart function.[7] However, data from a study conducted in a fish-consuming population in the Seychelles failed to find a similar connection.[8]

There has been considerable concern over the systemic absorption of mercury from *dental amalgam*, which typically contains between 40 and 70% of mercury. However, the quantity absorbed from amalgam fillings is reported to be relatively small[9,10] and current evidence suggests that the use of dental amalgam for tooth restoration is both safe and effective.[11-14] The main risks appear to be occupational exposure of dental staff and environmental pollution. Some patients with hypersensitivity to mercury (manifest most commonly as local lichenoid reactions) may benefit from removal of amalgam fillings.[15-17]

Ethylmercury is contained in *thiomersal*, which is used as a preservative in some vaccines for infants and children, thus representing a potential source of mercury exposure. The safety of these vaccines has been a matter of considerable debate worldwide for many years although it is now usually accepted that there is no evidence of neurotoxicity. However, some countries have phased out vaccines containing thiomersal in favour of alternative preservatives. For further details and references, see Thiomersal p. 1772.2.

The symptoms of *acrodynia* have been mistaken for those of phaeochromocytoma.[18-21]

1. Bluhm RE, *et al.* Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992; 11: 201–10.
2. Bluhm RE, *et al.* Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers part II: hyperchloraemia and genitourinary symptoms. *Hum Exp Toxicol* 1992; 11: 211–15.
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19. Velzeboer SCJM, *et al.* A hypertensive toddler. *Lancet* 1997; 349: 1810.
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21. Torres AD, *et al.* Mercury intoxication and arterial hypertension: report of two patients and review of the literature. Abstract: *Pediatrics* 2000; 105: 627. Full version: http://pediatrics.aappublications.org/cgi/reprint/105/3/e34.pdf (accessed 14/07/06)

Effects on the kidneys. The kidneys are one of the main sites for the accumulation of mercury in the body. All forms of mercury (liquid mercury, inorganic mercury, and organic mercury) may be toxic to the kidney although the inorganic forms are the most nephrotoxic.[1]

1. Zalups RK. Molecular interactions with mercury in the kidney. *Pharmacol Rev* 2000; 52: 113–43.

Hypersensitivity. Systemic contact dermatitis in a patient apparently sensitised by red, mercury-based tattoo pigments, developed when he ate raw swordfish and alfonsino, both renowned for high mercury levels.[1]

1. Tsuruta D, *et al.* A red tattoo and a swordfish supper. *Lancet* 2004; 364: 730.

Treatment of Adverse Effects

The treatment of **acute** mercury toxicity depends on the form of mercury, the route of exposure, and the dose. Supportive measures may be needed with all types of toxicity. Ingestion of elemental mercury seldom requires active treatment since it is poorly absorbed by this route, although inhalation or aspiration of elemental mercury vapour is a potentially serious problem. Poisoning due to organic mercury is difficult to treat and supportive measures are the mainstay of treatment. Acute exposure to mercury by injection requires mainly supportive therapy, although excision of the affected area has been recommended after subcutaneous or intramuscular injection. Mercurials on the skin should be removed by copious washing with soap and water; for contamination in the eye, irrigation with water at room-temperature for at least 15 minutes should be performed.

Acute oral poisoning due to inorganic mercury salts should be treated if appropriate by activated charcoal or gastric lavage to reduce absorption if within 1 hour of ingestion of a potentially life-threatening dose. Decontamination is not usually necessary after ingestion of small amounts such as elemental mercury from a thermometer. Some inorganic mercury compounds may be corrosive to the gastrointestinal tract when ingested, which can make gastrointestinal decontamination problematic; induction of emesis is not recommended. Gastric decontamination may be tried for organic mercury compounds, although the benefits are uncertain.

In severe cases of toxicity with all forms of mercury poisoning, chelation therapy may be required to facilitate the removal of mercury from the body. Unithiol (p. 1579.1) is the chelating agent of choice in the UK and should be considered in symptomatic patients with a blood-mercury concentration of 100 micrograms/litre, and in asymptomatic patients with a blood-mercury concentration of 200 micrograms/litre. Other chelating agents that may be used are succimer (p. 1576.3), dimercaprol (p. 1549.3), and penicillamine (p. 1567.1). The treatment of choice may vary in other countries depending on local policies and availability of the above chelating agents. Penicillamine may be associated with more adverse effects than other chelating agents and should be reserved for use when others are unavailable or not tolerated. Dimercaprol should be avoided in poisoning with metallic mercury or methylmercury because it may exacerbate neurological effects through redistribution of mercury to the brain from other sites.

Some centres start haemodialysis early in the course of treatment; others wait until renal failure develops. Giving a thiol resin complex to prevent the reabsorption of mercury from the bile has also been tried.

The management of **chronic** toxicity is generally symptomatic although chelation therapy has been used in some patients if the blood-mercury concentration is raised or the patient is symptomatic.

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3. Florentine MJ, Sanfilippo DJ. Elemental mercury poisoning. *Clin Pharm* 1991; 10: 213–21.
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7. Aaseth J, *et al.* Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate: a review. *Analyst* 1995; 120: 853–4.
8. Isik S, *et al.* Subcutaneous metallic mercury injection: early, massive excision. *Ann Plast Surg* 1997; 38: 645–8.
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Pharmacokinetics

There is little absorption of elemental mercury from globules in the gastrointestinal tract. The main hazard of elemental mercury is from absorption after inhalation of mercury vapour; this mercury is widely distributed before being oxidised to the mercuric form. Concentrations can be detected in the brain.

Soluble inorganic mercuric salts are absorbed from the gastrointestinal tract and can also be absorbed through the skin. The mercury is distributed throughout the soft tissues with high concentrations in the kidneys; it is mainly excreted in the urine and faeces with an elimination half-life of about 60 days, although it may take years to eliminate mercury from the brain; elimination from other tissues can take several months.

Organic alkyl mercury compounds are more readily absorbed from both the gastrointestinal and the respiratory tracts. They are widely distributed and can produce high concentrations in the brain. Alkyl mercury compounds are excreted in urine and in the faeces with extensive enterohepatic recycling. The biological half-life varies but is longer than that of inorganic mercury.

Organic mercury, and to some extent inorganic mercury, diffuse across the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Coldophthal; Nasenol; *Ger.*: Iscador c Hg; Schnupfencreme; Weleda Nasenol; *Spain*: Oftalmol Ocular.

Homoeopathic Preparations. *Austral.*: Earache Relief†; Elimitona Slim & Detox; Elimitona; Joint & Muscle Oral Spray†; Pain & Fever Relief; Respatona Sore Throat; Teething Relief; *Austria*: Apozema Apis compositum; Asinis; Delufen; Echinacea-Cosmoplex; Euphorbium Compositum; Exangina†; Globuli gegen Halsweh Nr 2; Globuli gegen Hautausschlage; Globuli gegen Schnupfen Nr 3; Lymphdiaral; Lymphdiaral; Meditonsin; Metasinusit; Nebenhohlen-Tropfen Nr 26†; Ohrentropfen Similasan; Otovowen; Rhododendroneel; Tonsan akut; Tonsillopas; Tonsiotren; Traumeel; Vocara; Zom; *Canad.*: Cough & Cold; Diarrex; Earache; Euphorbium Compositum; Homeovox; Hylands Sore Throat; Roxalia; Sinus Ease; Sinuspax†; Sore Throat; *Chile*: Bioactiv H; *Cz.*: Angin-Heel S; Traumeel; *Fr.*: Aftosium; Calendula Complexe No 89; Dolistamine†; Hepatodrainol; Homeodose 24†; Homeogene 9; Homeovox; Mercurius Cyanatus Complexe No 43†; Mercurius Solubilis Complexe No 39; Phytogargarisme†; Silicea Complexe No 11; Sinuspax; *Ger.*: Anovin; Cefasept N; Cefasept†; Cefasinu; Entzundungstropfen; Euphorbium comp SN; Hevertotox; Humoval; Infihepan; Lymphaden Complex; Lymphaden; Lymphdiaral Halstabletten; Lymphdiaral sensitive N; Lymphdiaral; Mato; Meditonsin; Mercurell; Muco-cyl L Ho-Len-Complex; Mullersche Tabletten; Otovowen; Pyrogenium; Rufebran lympho†; Schworosin; Sinasal; Sinfrontal; Sinuselect N; Sinusitis Hevert SL; Sinusitis Hevert†; Sinusitis-Weliplex†; Tonsillopas; Tonsillosyx; Tonsiotren H; Traumeel S; Zahnungstropfen Escatitona; *Hung.*: Angin-Heel; Homeogene 9; Homeovox; Naso-Heel S; Osteoheel; Traumeel; *Neth.*: Discus comp H; Euphorbium comp; Hepalite; Hepatodrainol†; Homeogene 9†; Homeovox; Lymphdiaral; Mercurius-Heel; Myamolite; Oteel H; Ricura; Rinileen†; Tonsiotreen; Traumeel H; Traumeel S; *Port.*: Hepatodrainol; Homeogene 9; Homeovox; *Rus.*: Aphlubin-Naze (Афлубин-Назе); Asinis (Асинис); Belladonna-Plus (Беллядонна-Плюс); Cinnabsin (Циннабсин); Delufen (Делуфен); Homeovox (Гомеовокс); Mercure-Plus (Меркур-Плюс); Plantago-Plus (Плантаго-Плюс); Tonsan-Akut (Тонзан-акут); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); Vocara (Вокара); *S.Afr.*: Euphorbium Compositum S†; Traumeel S; Zinnober D6†; *Switz.*: A Vogel pour les sinus; Homeogene 9; metasinusit; Osteoheel; Sinfrontal; Sinusin; Sinuspax†; Traumeel; *UK*: Catarrh Cream; Oleum Rhinale; *Ukr.*: Asinis (Асинис); Cinnabsin (Циннабсин); Delufen (Делуфен); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); Vocara (Вокара); *Venez.*: Traumeel.

Mescaline

Mescalina; Mescalinum; Meskaliini; Meskalin.
3,4,5-Trimethoxyphenethylamine.
$C_{11}H_{17}NO_3$=211.3
CAS — 54-04-6.
UNII — RHO99102VC.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for mescaline or peyote:

Bad seed; Beans; Big chief; Black button; Blue caps; Britton; Buttons; Cactus; Cactus buttons; Cactus head; Chief; Crystal; Dusty; Full moon; Green button; Half moon; Hikori; Hikula; Hikuli; Hyatari; Indians; M; Mesc; Mesca; Mescal; Mescalito; Mescap; Mescy; Mese; Mess; Mezc; Moon; Musk; Nubs; P; Peyote; Peyotl; Pixie sticks; San Pedro; Seni; Shaman; Topi; Tops.

Profile

Mescaline is an alkaloid obtained from the cactus *Lophophora williamsii* (*Anhalonium williamsii, A. lewinii*) (Cactaceae), which grows in the northern regions of Mexico. The cactus is known in those areas by the Aztec name 'peyote' or 'peyotl' and dried slices of the cactus are called 'mescal buttons'.

Mescaline produces hallucinogenic and sympathomimetic effects similar to those produced by lysergide (see p. 2547.1), but it is less potent. Its effects last for up to 12 hours. It has no therapeutic use. Both Mexican and North American Indians have used peyote in religious ceremonies on account of its hallucinogenic activity.

Botulism. Peyote consumed during a ceremonial ritual was believed to have caused botulism in three men.[1] The sample was found to contain type B botulinum toxin when assayed.

1. Hashimoto H, *et al.* Botulism from peyote. *N Engl J Med* 1998; 339: 203–4.

Mesoglycan Sodium

Mesoglicano sódico; Sodium Mesoglycan.

Profile

Mesoglycan sodium is a mucopolysaccharide complex (glycosaminoglycan) extracted from calf aorta, containing mainly suleparoid (heparan sulfate) (p. 1507.2) and dermatan sulfate (p. 1350.3). It has been claimed to have antithrombotic, antiplatelet, and antihyperlipidaemic properties.

References.

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3. Arosio E, *et al.* A placebo-controlled, double-blind study of mesoglycan in the treatment of chronic venous ulcers. *Eur J Vasc Endovasc Surg* 2001; 22: 365–72.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Prisma; *Port.*: Prisma.

Metamfepramone Hydrochloride (rINNM) ⊗

Dimepropion Hydrochloride (BANM); Hidrocloruro de metanfepramona; Métamfépramone, Chlorhydrate de; Metamfepramoni Hydrochloridum; Metamfepyramone Hydrochloride; Metanfepramona, hidrocloruro de; Метамфепрамона Гидрохлорид.
2-Dimethylaminopropiophenone hydrochloride.
$C_{11}H_{15}NO,HCl$=213.7
CAS — 15351-09-4 (metamfepramone); 10105-90-5 (metamfepramone hydrochloride).
UNII — 6Y816E97O1.

Profile

Metamfepramone, the dimethyl analogue of diethylpropion (p. 2321.1) and a derivative of cathinone (p. 2318.2), is a sympathomimetic that has been used as the hydrochloride in the treatment of hypotension and in preparations for the symptomatic relief of the common cold. It was formerly used as an anorectic agent. It is also subject to abuse (see Abuse, under Catha, p. 2318.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Tempil N†.

Metergoline (BAN, rINN)

FI-6337; MCE; Metergoliini; Metergolin; Metergolina; Métergoline; Metergolinum; Methergoline; Метаролин.
Benzyl (8S,10S)-(1,6-dimethylergolin-8-ylmethyl)carbamate.
$C_{25}H_{29}N_3O_2$=403.5
CAS — 17692-51-2.
ATC — G02CB05.
ATC Vet — QG02CB05.
UNII — 150T393LY5.

Profile

Metergoline, an ergot derivative, is a dopamine agonist with actions and uses similar to those of bromocriptine (p. 895.3). It is also a serotonin antagonist. Metergoline has been used similarly to bromocriptine in disorders associated with hyperprolactinaemia in usual oral doses of 12 mg daily in divided doses; up to 24 mg daily has been given in hyperprolactinaemic men. It has also been used orally to inhibit lactation, for the treatment of gastrointestinal disorders, and for the prophylaxis of migraine and other vascular headaches.

Hyperprolactinaemia and prolactinomas. Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p. 2252.2). Metergoline has been tried in patients intolerant of bromocriptine.[1] In this report metergoline lowered plasma-prolactin concentrations, although not to normal, in 3 men and 8 women with hyperprolactinaemia. Galactorrhoea was abolished and/or a regular menstrual cycle established in 5 of the women. Prolactin concentrations and symptoms were unchanged in 3 further women with normoprolactinaemic galactorrhoea.

1. Casson IF, *et al.* Intolerance of bromocriptine: is metergoline a satisfactory alternative? *BMJ* 1985; 290: 1783–4.

Migraine. Although metergoline has been used in some countries for the prophylaxis of migraine (p. 670.3) it is not usually considered to be the drug of choice or even one of the main alternatives.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Liserdol; *Ital.*: Liserdol.

Metesculetol Sodium (rINNM)

Metesculetol sódico; Métesculétol Sodique; Methesculétol Sodique; Methyl-4-esculetol Monoethanoate Sodium; Natrii Metesculetolum; Натрий Метэскулетон.
[(7-Hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-6-yl)oxy] acetate sodium.
$C_{12}H_9NaO_6$=272.2
CAS — 52814-39-8 (metesculetol); 53285-61-3 (metesculetol sodium).

Profile

Metesculetol is included in preparations for peripheral vascular disorders and haemorrhoids. It is also present in some oral hygiene preparations. Metescufylline is a compound of metesculetol and etamiphylline (p. 1208.2) that has been given orally for its reputed vasoprotectant effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Diencil; Parogencyl Bi-Actif†; Vitis Encias Colutorio; Vitis Encias Pasta; *Fr.*: Intrait de Marron d'Inde P; Parogencyl prevention gencives†; Parogencyl sensibilite gencives†; Veinotonyl; *Hong Kong*: Pyodontyl†; *Ital.*: Parogencyl; *Mon.*: Pluon.

Methacholine Chloride (BAN, rINN)

Acetyl-β-methylcholine Chloride; Amechol Chloride; Cloruro de metacolina; Metacolina, cloruro de; Méthacholine, Chlorure de; Methacholini Chloridum; Methacholinium Chloratum; Метахолиния Хлорид.
(2-Acetoxypropyl)trimethylammonium chloride.
$C_8H_{18}ClNO_2$=195.7
CAS — 55-92-5 (methacholine); 62-51-1 (methacholine chloride).
UNII — 0W5ETF9M2K.

Pharmacopoeias. In *Fr.*, *Swiss*, and *US*.

USP 36: (Methacholine Chloride). Colourless or white crystals, or a white crystalline powder. It is odourless or has a slight odour, and is very hygroscopic. Soluble 1 in 1.2 of water, 1 in 1.7 of alcohol, and 1 in 2.1 of chloroform. Its solutions are neutral to litmus. Store in airtight containers.

Uses and Administration

Methacholine is a quaternary ammonium parasympathomimetic with the muscarinic actions of acetylcholine (p. 2003.2). It is hydrolysed by acetylcholinesterase at a considerably slower rate than acetylcholine and is more resistant to hydrolysis by non-specific cholinesterases so that its actions are more prolonged.

Inhalation of nebulised solutions of methacholine chloride are used to provoke bronchoconstriction in the diagnosis of bronchial airway hypersensitivity (but see Precautions, below).

Methacholine chloride has been used in eye drops as a miotic for diagnostic purposes.

References.
1. Crapo RO, *et al.* Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000; 161: 309–29. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/161/1/309.pdf (accessed 30/05/08)
2. Swartz E, Lang D. When should a methacholine challenge be ordered for a patient with suspected asthma? *Cleve Clin J Med* 2008; 75: 37–40.

Adverse Effects and Treatment

As for Acetylcholine Chloride, p. 2003.2. Severe adverse cholinergic effects have followed the oral and parenteral use of methacholine and these routes are no longer used.

Precautions

As for Neostigmine, p. 688.3.

Methacholine has the potential to produce severe bronchoconstriction and it should not be used for inhalation challenge tests in patients with clinically apparent asthma, wheezing, or poor pulmonary function.

Methacholine should not be given orally or parenterally.

Interactions

As for Neostigmine, p. 688.3. Methacholine is slowly hydrolysed by acetylcholinesterase, and its effects are markedly enhanced if used after anticholinesterases.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Provocholine; *Israel*: Provocholine; *Spain*: Provocholine; *USA*: Mecholyl; Provocholine.

Methiosulfonium Chloride

Methylmethionine Sulfonium Chloride; Metiosulfonio, cloruro de; Vitamin U; Метиосульфония Хлорид.
(3-Amino-3-carboxypropyl)dimethylsulphonium chloride.
$C_6H_{14}ClNO_2S$=199.7
CAS — 1115-84-0.
ATC — A02BX04.
ATC Vet — QA02BX04.
UNII — G9CUR2204U.

Profile

Methiosulfonium chloride has been used for its reputed protective effect on the liver and gastrointestinal mucosa. The bromide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Cabagin-U.

Multi-ingredient Preparations. *China*: Aoweishu (澳谓舒); Rudd-U (立愉); Wei Tai Kang (谓泰康); *Jpn*: Cabagin S New; Cabagin†; Cabe 2†; The Guard Seichojo; *Singapore*: Weisen-U.

Methyl Fluorosulfate

Fluorosulfato, metilo de; Magic Methyl; Methyl Fluorosulphate; Methyl Fluorosulphonate.
CH_3FO_3S=114.1
CAS — 421-20-5.
UNII — N01SVFJ94Z.

Profile

Methyl fluorosulfate has been used as a laboratory methylating agent. Pulmonary oedema has occurred after inhalation, and concern has been expressed concerning possible carcinogenicity.

Methylenedioxycinnamic Acid

Метилендиоксикоричная Кислота.
3,4-Methylenedioxycinnamic acid.
$C_{10}H_8O_4$=192.2
CAS — 2373-80-0.

Profile

Methylenedioxycinnamic acid and its potassium salt have been used in preparations for the treatment of liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vacuobil.

Multi-ingredient Preparations. *Arg.*: Vacuobil Plus.

Methylhydroxyquinoline Metilsulfate

Methylhydroxyquinoline Methylsulphate; Metilhidroxiquinolina, metilsulfato de; Метилгидроксихинолина Метилсульфат.
1-Methyl-8-hydroxyquinolinium methyl sulphate.
$C_{10}H_{10}NO.CH_3O_4S$=271.3
CAS — 19104-24-6.

Profile

Methylhydroxyquinoline metilsulfate has been used topically to treat eye irritation.

Methylmethacrylate

Metacrilato de metilo; Méthacrylate de méthyle; Methyl Methacrylate; Methylis methacrylas; Метилметакрилат.
Methyl 2-methylacrylate; Methyl 2-methylpropenoate.
$C_5H_8O_2$=100.1
CAS — 80-62-6.
UNII — 196OC77688.

Uses and Administration

Methylmethacrylate forms the basis of acrylic bone cements used in orthopaedic surgery. A liquid consisting chiefly of methylmethacrylate monomer with a polymerisation initiator is mixed with a powder consisting of polymethylmethacrylate (PMMA) or a methylmethacrylate ester copolymer. The reaction is exothermic. Barium sulfate or zirconium dioxide may be added as a contrast medium. PMMA beads containing gentamicin have been implanted for the prophylaxis and treatment of bone infections and some soft-tissue infections. Bone cements containing antibacterials such as gentamicin or erythromycin are also available.

PMMA has also been used as a material for intra-ocular lenses, for denture bases, as a cement for dental prostheses, and in composite resins for dental restoration.

Several polymers based on methacrylic acid are used in pharmaceutical technology mainly as film coating agents and binders.

Ph. Eur. 8 includes:
- Ammonio Methacrylate Copolymer (Type A) (a copolymer of acrylic and methacrylic acid esters)
- Ammonio Methacrylate Copolymer (Type B) (a copolymer of acrylic and methacrylic acid esters)
- Basic Butylated Methacrylate Copolymer
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:1)
- Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)
- Methacrylic Acid-Methyl Methacrylate Copolymer (1:2)

USNF 31 includes:
- Methacrylic Acid Copolymer (a copolymer of methacrylic acid and an acrylic or methacrylic ester)
- Amino Methacrylate Copolymer
- Ammonio Methacrylate Copolymer
- Ethyl Acrylate and Methyl Methacrylate Copolymer
- Methacrylic Acid and Ethyl Acrylate Copolymer
- Partially-Neutralized Methacrylic Acid and Ethyl Acrylate Copolymer
- Methacrylic Acid and Methyl Methacrylate Copolymer

Bone disorders. Polymethylmethacrylate bone cements are used in orthopaedics; typically they are injected percutaneously into vertebral fractures or lesions to relieve pain and stabilise the damaged vertebra, and are used in joint replacement.[1-7] The technique has been used in the treatment of metastatic bone lesions and myeloma (p. 700.3 and p. 699.2) as well as for vertebral compression fractures due to osteoporosis (p. 1168.1). Complications[5,8-11] are uncommon but may include both local and systemic effects (including pulmonary embolism) due to leakage of the cement and sudden drop in blood pressure, probably due to the monomer.

1. Barr JD, *et al.* Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine* 2000; 25: 923–8.
2. Lingar L. Percutaneous polymethacrylate vertebroplasty. *Radiol Technol* 2004; 76: 109–13.
3. Burton AW, *et al.* Vertebroplasty and kyphoplasty: a comprehensive review. *Neurosurg Focus* 2005; 18: e1. Available at: http://www.medscape.com/viewarticle/501670 (accessed 11/11/09)
4. Suresh SP, Whitehouse RW. Vertebroplasty and kyphoplasty. *J Br Menopause Soc* 2005; 11: 28–32.
5. Guglielmi G, *et al.* Percutaneous vertebroplasty: indications, contraindications, technique, and complications. *Acta Radiol* 2005; 46: 256–68.
6. Hochmuth K, *et al.* Percutaneous vertebroplasty in the therapy of osteoporotic vertebral compression fractures: a critical review. *Eur Radiol* 2006; 16: 998–1004.
7. Webb JCJ, Spencer RF. The role of polymethylmethacrylate bone cement in modern orthopaedic surgery. *J Bone Joint Surg Br* 2007; 89: 851–7.
8. Laredo JD, Hamze B. Complications of percutaneous vertebroplasty and their prevention. *Semin Ultrasound CT MR* 2005; 26: 65–80.
9. Barragan-Campos HM, *et al.* Percutaneous vertebroplasty for spinal metastases: complications. *Radiology* 2006; 238: 354–62.
10. Health Canada. Complications associated with the use of bone cements in vertebroplasty and kyphoplasty procedures (issued 30th May, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bone_cement-ciment_acrylique_nth-ash_2_e.pdf (accessed 30/5/08)
11. Venmans A, *et al.* Frequency and outcome of pulmonary polymethylmethacrylate embolism during percutaneous vertebroplasty. *AJNR Am J Neuroradiol* 2008; 29: 1983–5.

Adverse Effects and Precautions

Occupational exposure to methylmethacrylate monomer vapour during preparation of the bone cement may irritate the respiratory tract, eyes, and skin. Cases of occupational asthma have been reported. Contact dermatitis, dizziness, nausea and vomiting may also occur. Methylmethacrylate monomer may be harmful to the liver.

Methylmethacrylate monomer acts as a peripheral vasodilator and has caused hypotension and, rarely, cardiac arrest and death when absorbed during the use of polymethylmethacrylate (PMMA) as a bone cement during orthopaedic surgery (see also Bone Disorders under Uses and Administration, above). Other adverse effects associated with the use of PMMA as a bone cement include thrombophlebitis, pulmonary embolism, haemorrhage, haematoma, short-term irregularities in cardiac conduction, cerebrovascular accident, compression of the spinal cord and/or nerve roots, and new fractures in adjacent non-augmented vertebrae. Recommendations when using PMMA include monitoring with high quality imaging systems to detect leakage, and close monitoring of blood pressure during and immediately after the procedure.

References.
1. Leggat PA, Kedjarune U. Toxicity of methyl methacrylate in dentistry. *Int Dent J* 2003; 53: 126–31.
2. Leggat PA, *et al.* Surgical applications of methyl methacrylate: a review of toxicity. *Arch Environ Occup Health* 2009; 64: 207–12.

Effects on the nervous system. Sensory polyneuropathy has been reported in a dental technician after occupational exposure to methylmethacrylate monomer.[1]

1. Sadoh DR, *et al.* Occupational exposure to methyl methacrylate monomer induces generalised neuropathy in a dental technician. *Br Dent J* 1999; 186: 380–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Palacos R†; *Ger.*: Biomet Bone Cement R; Biomet Plus Bone Cement†; flint; SmartSet HV; *Gr.*: Palacos; *Port.*: Septopal; *Singapore*: Palacos R; *Thai.*: Biomet; Palacos R†; *UK*: Palacos R.

Multi-ingredient Preparations. *Austral.*: Palacos E with Garamycin†; Palacos R with Garamycin†; Septopal†; *Austria*: Septopal; *Belg.*: Septopal; *Braz.*: Septopal; *Chile*: Palacos E con Gentamicina†; Palacos R con Gentamicina†; Perlas De PMMA con Gentamicina†; *China*: Septopal (塞透派勒); *Denm.*: Septopal†; *Fin.*: Septopal; *Fr.*: Septopal†; *Ger.*: Epiglu; Heraeus PMMA Kette G; Palasept G†; Refobacin Bone Cement R; Refobacin Plus Bone Cement; Refobacin Revision; Septopal; SmartMix Cemvac GHV; SmartSet GHV; *Gr.*: Palacos R with Gentamycin; Septopal; *Hong Kong*: Septopal†; *Hung.*: Septopal†; *India*: Septopal†; *Irl.*: Epiglu†; *Neth.*: Septopal; *Norw.*: Septopal; *NZ*: Antibiotic Simplex; CMW Gentamicin; Palacos with Garamycin; Smartmix; Smartset; Vacu-Mix Plus with CMW gentamicin; *Philipp.*: Septopal; *S.Afr.*: Palacos R with Garamycin; Septopal; *Singapore*: Refobacin Bone Cement R†; Septopal; *Switz.*: Septopal; *Thai.*: Refobacin Bone Cement R; Septopal; *UK*: Epiglu; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal.

Metochalcone *(rINN)*

CB-1314; Methochalcone; Metocalcona; Métochalcone; Metochalconum; Trimethoxychalcone; Метохалкон.
2′,4,4′-Trimethoxychalcone.
$C_{18}H_{18}O_4$=298.3
CAS — 18493-30-6.
UNII — 1754ZE4075.

Profile

Metochalcone has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Neocolan†.

Metocinium Iodide (pINN)

Ioduro de metocinio; Metocinii iodidum; Métocinium, Iodure de; Метоциния Йодид.

(2-Hydroxyethyl)trimethylammonium iodide benzilate.

$C_{19}H_{24}INO_3$=441.3.

CAS — 2424-71-7.

UNII — R115BP9F2B.

Profile

Metocinium iodide is used as an antispasmodic.

Metyrapone (BAN, USAN, rINN)

Metirapon; Metirapona; Metyrapon; Métyrapone; Metyraponi; Metyraponum; Su-4885 (metyrapone tartrate); Метирапон.

2-Methyl-1,2-di(3-pyridyl)propan-1-one.

$C_{14}H_{14}N_2O$=226.3.

CAS — 54-36-4.

ATC — V04CD01.

ATC Vet — QV04CD01.

UNII — ZS9KD92H6V.

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

BP 2014: (Metyrapone). A white to light amber crystalline powder with a characteristic odour. M.p. 50 degrees to 53 degrees. Sparingly soluble in water; freely soluble in alcohol and in chloroform; it dissolves in dilute mineral acids. Protect from light.

USP 36: (Metyrapone). A white to light amber, fine, crystalline powder, having a characteristic odour. It darkens on exposure to light. Sparingly soluble in water; soluble in chloroform and in methyl alcohol; forms water-soluble salts with acids. Store in airtight containers. Protect from heat and light.

Uses and Administration

Metyrapone inhibits the enzyme 11β-hydroxylase responsible for the synthesis of the glucocorticoids cortisone and hydrocortisone (cortisol) as well as aldosterone from their precursors. The consequent fall in the plasma concentrations of circulating glucocorticoids stimulates the anterior pituitary gland to produce more corticotropin. This, in turn, stimulates the production of more 11-deoxycortisol and other precursors which are metabolised in the liver and excreted in the urine where they can be measured. Metyrapone is therefore used as a test of the feedback hypothalamic-pituitary mechanism in the differential diagnosis of ACTH-dependent Cushing's syndrome, although the dexamethasone suppression test (p. 1632.1) may be preferred.

After demonstration of the responsiveness of the adrenal cortex, metyrapone is given orally, usually in a dose of 750 mg every 4 hours for 6 doses. Taking doses with milk or after a meal may minimise the gastrointestinal adverse effects of metyrapone. For doses in children, see below. In patients with a normally functioning pituitary gland excretion of 17-hydroxycorticosteroids is increased two- to fourfold and that of 17-ketosteroids about twofold.

Metyrapone is also used in the management of Cushing's syndrome (below) when doses may range from 250 mg to 6 g daily.

Since metyrapone inhibits the synthesis of aldosterone it has been used to treat some cases of resistant oedema; it is given with a glucocorticoid to suppress the normal corticotropin response to low plasma concentrations of glucocorticoids. The suggested usual dosage of metyrapone in resistant oedema is 3 g daily in divided doses.

Metyrapone tartrate has also been used.

Administration in children. The oral dose of metyrapone in children aged 1 month and over for the differential diagnosis of ACTH-dependent Cushing's syndrome is 15 mg/kg, with a minimum dose of 250 mg, every four hours for 6 doses.

Cushing's syndrome. Cushing's syndrome is the result of a chronic excess of glucocorticoids.[1] It may be independent of the secretion of adrenocorticotrophic hormone (ACTH; corticotropin), either due to an adrenal tumour secreting cortisol, or to exogenous corticosteroids, or it may be ACTH-dependent, such as Cushing's disease proper, which is caused by excessive ACTH secretion from a pituitary adenoma; other ACTH-dependent forms may be due to pituitary hyperplasia, or an ectopic ACTH-secreting tumour elsewhere—usually bronchus or lung cancer. About two-thirds of all cases are due to Cushing's disease, which is 8 times more common in women than men.

Symptoms may develop insidiously over several years and include obesity, particularly of the trunk, rounding of the face, atrophy of the skin leading to striae, poor wound healing, muscle weakness, osteoporosis, hypertension, diabetes mellitus, and depression and other psychological disturbances. Hypokalaemia is rare in Cushing's disease but common in other forms of the syndrome. Women may have hirsutism due to adrenal androgen secretion, and both sexes may develop hypogonadism and loss of libido.

Diagnosis of Cushing's syndrome can be problematic because no test is wholly reliable.[1-5] Where there is suspicion, options for initial screening include measurement of urinary cortisol, late-night salivary cortisol, midnight plasma-cortisol, and overnight low-dose dexamethasone suppression testing. A dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism. Once a diagnosis of Cushing's syndrome has been made, plasma-ACTH measurements are used to distinguish between ACTH-dependent and ACTH-independent forms. High-dose dexamethasone suppression testing and corticorelin stimulation testing have been used to differentiate between pituitary and ectopic ACTH-dependent Cushing's syndrome, but they both have disadvantages and their usefulness has been debated. The conclusion from one review[6] was that measurement of urinary free cortisol and the dexamethasone suppression test have most evidence supporting their use while there is limited evidence supporting the use of salivary and serum midnight cortisol tests. For further discussion of dexamethasone suppression testing, see p. 1632.1, and for corticorelin stimulation testing, see p. 1628.2. Imaging techniques and sampling of central (petrosal) venous blood are additional procedures that may be used for localising tumours.

Appropriate **treatment** depends on accurate identification of the cause of the syndrome.[1] The usual treatment[7] in Cushing's disease is transsphenoidal resection of the tumour, which when carried out by an experienced surgeon produces a successful response in the majority of patients. Pituitary radiotherapy is slower than surgery to take effect, produces a lower remission rate, and is more likely to produce hypopituitarism. It is therefore usually used as second-line therapy when initial surgery has not been curative and a second operation is considered unsuitable. If pituitary surgery or radiotherapy fails, bilateral adrenalectomy may be considered (although this has some risks including that of Nelson's syndrome due to hyperactivity of residual pituitary tumour). Patients who undergo such surgery require glucocorticoid and mineralocorticoid replacement therapy for life. Surgery is also the treatment of choice for a resectable adrenal tumour or ectopic ACTH-secreting tumour; even where there is metastasis it may be useful in moderating symptoms.

Pasireotide, which has a high affinity for somatostatin receptor subtype 5, may be used for medical treatment of ACTH-secreting pituitary adenoma when surgery is not possible or has failed.[8] Several other drugs have been used in patients with Cushing's disease, but their role appears to be mainly adjuvant.[1,7,9] Those acting at the hypothalamic-pituitary level, aimed at reducing ACTH secretion, do not seem to be of much value; there have been occasional reports of benefit with bromocriptine, cyproheptadine, and sodium valproate. Drugs that inhibit steroid synthesis in the adrenal gland are more effective, and include mitotane, metyrapone, and ketoconazole. These may be used to control severe complications quickly, prepare patients for surgery, or provide cover while radiotherapy takes effect. Mifepristone acts as a glucocorticoid receptor antagonist, and has been used successfully in a few patients with Cushing's syndrome. Etomidate can be useful for acute control of hypercortisolaemia if the oral route is not available.

In patients with the ectopic ACTH syndrome in whom surgery is unsuitable or ineffective, chemotherapy aimed at the primary tumour is the treatment of choice but is likely to be only palliative. Inhibitors of steroid synthesis can be used to control symptoms, and somatostatin analogues such as octreotide may decrease ACTH secretion by ectopic tumours that have somatostatin receptors.[1]

Surgery is the preferred treatment for an adrenal tumour but, although this is usually curative for adrenal adenoma, it is less successful for adrenal carcinoma.[1]

In patients who are successfully treated for Cushing's syndrome, adrenocortical replacement therapy (see p. 1600.2) is usually required until the hypothalamic-pituitary-adrenal axis recovers normal function, a process which may take many months.

1. Newell-Price J, *et al.* Cushing's syndrome. *Lancet* 2006; 367: 1605–17.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; 138: 980–91.
3. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; 88: 5593–5602.
4. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab* 2006; 91: 3746–53.
5. Nieman LK, *et al.* The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93: 1526–40. Also available at: http://www.endo-society.org/guidelines/final/upload/Cushings_Guideline.pdf (accessed 06/08/08)
6. Elamin MB, *et al.* Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. *J Clin Endocrinol Metab* 2008; 93: 1553–62.
7. Biller BMK, *et al.* Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008; 93: 2454–62.
8. Colao A, *et al.* Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med* 2012; 366: 914–24. Correction. *ibid.*; 367: 780.
9. Nieman LK. Medical therapy of Cushing's disease. *Pituitary* 2002; 5: 77–82.

Adverse Effects

Metyrapone may give rise to nausea and vomiting, abdominal pain, headache, sedation, dizziness, hypotension, and hypersensitivity rashes. Hypoadrenalism, hirsutism, and bone marrow depression may occur rarely. Long-term use of metyrapone can cause hypertension.

Alopecia. Reports of alopecia[1,2] associated with administration of metyrapone for Cushing's syndrome.

1. Harris PL. Alopecia associated with long-term metyrapone use. *Clin Pharm* 1986; 5: 66–8.
2. Harries-Jones R, Overstall P. Metyrapone-induced alopecia. *Postgrad Med J* 1990; 66: 584.

Precautions

Metyrapone should be used with extreme caution, if at all, in patients with gross hypopituitarism or with reduced adrenal secretory activity because of the risk of precipitating acute adrenal failure. Thyroid dysfunction or liver cirrhosis may alter the response to metyrapone.

Dizziness and sedation may affect the performance of skilled tasks such as driving.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies metyrapone 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

Phenytoin is reported to increase the metabolism of metyrapone; doubling the dose of metyrapone may counteract the interaction. Drugs reported to interfere with the metyrapone test include antidepressants such as amitriptyline, antithyroid drugs, antipsychotics such as chlorpromazine, barbiturates, corticosteroids, cyproheptadine, and hormones that affect the hypothalamic-pituitary axis such as oestrogens and progestogens.

Pharmacokinetics

Metyrapone is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after ingestion. It is metabolised by rapid reduction to metyrapol and excreted in the urine mainly as glucuronide conjugates of metyrapone and metyrapol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Metopirone; *Fr.*: Metopirone; *Gr.*: Metopirone; *Hong Kong*: Metopirone; *Irl.*: Metopirone; *Israel*: Metopirone; *Neth.*: Metopiron; *NZ*: Metopirone; *Switz.*: Metopirone; *UK*: Metopirone; *USA*: Metopirone.

Pharmacopoeial Preparations

BP 2014: Metyrapone Capsules;
USP 36: Metyrapone Tablets.

Miglustat (BAN, USAN, rINN)

Butyldeoxynojirimycin; n-Butyl-deoxynojirimycin; Miglustaatti; Miglustatum; OGT-918; OXAiDS; SC-48334; Миглустат.

1,5-(Butylimino)-1,5-dideoxy-D-glucitol;(2*R*,3*R*,4*R*,5*S*)-1-Butyl-2-(hydroxymethyl)piperidine-3,4,5-triol.

$C_{10}H_{21}NO_4$=219.3.

CAS — 72599-27-0.

ATC — A16AX06.

ATC Vet — QA16AX06.

UNII — ADN35497AZ.

Uses and Administration

Miglustat is an inhibitor of the enzyme glucosylceramide synthase, responsible for the first step in the synthesis of glucosylceramide and most other glycolipids. It is used to help prevent the accumulation of glucosylceramide in patients with mild to moderate type 1 Gaucher disease (p. 2433.3) who cannot be treated with enzyme replacement therapy. It is also used for the treatment of

progressive neurological manifestations of Niemann-Pick type C disease. The initial dose in type 1 Gaucher disease is 100 mg orally 3 times daily; reduction to 100 mg once or twice daily may be necessary in some patients because of diarrhoea. The dose for the treatment of Niemann-Pick type C disease is 200 mg orally three times daily; temporary dose reduction may be necessary in some patients because of diarrhoea. For doses to be used in children, see below. For details of reduced doses in patients with renal impairment, see below.

References.
1. McCormack PL, Goa KL. Miglustat. *Drugs* 2003; **63**: 2427–34.
2. Weinreb NJ, *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80**: 223–9.
3. Giraldo P, *et al.* Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease. *Haematologica* 2006; **91**: 703–6.
4. Elstein D, *et al.* Oral maintenance clinical trial with miglustat for type I Gaucher disease: switch from or combination with intravenous enzyme replacement. *Blood* 2007; **110**: 2296–2301.
5. Patterson MC, *et al.* Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007; **6**: 765–72.

Administration in children. Doses of miglustat given orally for the treatment of Niemann-Pick type C disease in children are adjusted on the basis of body-surface:
- greater than 1.25 m^2: 200 mg three times daily
- between 0.88 and 1.25 m^2: 200 mg twice daily
- between 0.73 and 0.88 m^2: 100 mg three times daily
- between 0.47 and 0.73 m^2: 100 mg twice daily
- equal to or less than 0.47 m^2: 100 mg daily

Administration in renal impairment. The initial dose of miglustat given orally should be reduced in renal impairment according to the patient's creatinine clearance (CC). For the treatment of **type 1 Gaucher disease**, reduced doses are:
- CC 50 to 70 mL/minute per 1.73 m^2: 100 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg once daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended

For the treatment of **Niemann-Pick type C disease**, reduced doses are:
- CC 50 to 70 mL/minute per 1.73 m^2: 200 mg twice daily
- CC 30 to 50 mL/minute per 1.73 m^2: 100 mg twice daily
- CC less than 30 mL/minute per 1.73 m^2: not recommended Doses for Niemann-Pick type C disease in children below the age of 12 years with renal impairment should be adjusted for body-surface. See Administration in Children, above for doses in children with normal renal function.

Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances, weight loss, tremor, dizziness, headache, cramps in legs, and visual disturbances are frequent in patients receiving miglustat, and some patients may have paraesthesias, peripheral neuropathy, or thrombocytopenia. Studies in *animals* have indicated an effect on spermatogenesis; male patients should not attempt conception during, or for 3 months after stopping, treatment. Care is required in renal impairment.

Pharmacokinetics

Miglustat is rapidly absorbed after oral doses and peak plasma concentrations occur in about 2 hours. It is mainly excreted in the urine with some also excreted in the faeces; the average elimination half-life is 6 to 7 hours.

Food. The average peak plasma concentration was reduced by 37% when miglustat was taken with food by 24 healthy subjects. However, there was no clinically significant effect on the extent of absorption (area under the curve was decreased by 14%).[1] Licensed product information states that miglustat may be taken with or without food.

1. van Giersbergen PLM, Dingemanse J. Influence of food intake on the pharmacokinetics of miglustat, an inhibitor of glucosylceramide synthase. *J Clin Pharmacol* 2007; **47**: 1277–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zavesca; ***Austria***: Zavesca; ***Belg.***: Zavesca; ***Braz.***: Zavesca; ***Canad.***: Zavesca; ***Cz.***: Zavesca; ***Denm.***: Zavesca; ***Fin.***: Zavesca; ***Fr.***: Zavesca; ***Ger.***: Zavesca; ***Gr.***: Zavesca; ***Hung.***: Zavesca; ***Irl.***: Zavesca; ***Israel***: Zavesca; ***Ital.***: Zavesca; ***Jpn***: Brazaves; ***Neth.***: Zavesca; ***Norw.***: Zavesca; ***NZ***: Zavesca; ***Pol.***: Zavesca; ***Port.***: Zavesca; ***Rus.***: Zaveska (Завеска); ***Spain***: Zavesca; ***Swed.***: Zavesca; ***Switz.***: Zavesca; ***UK***: Zavesca; ***USA***: Zavesca.

Dementholised Mint Oil

Csökkentett mentoltartalmú mezei mentaolaj (partly dementholised mint oil); Menta, aceite esencial desmentolado de; Mentha arvensis, huile essentielle partiellement démentholée de (mint oil, partly dementholised); Menthae arvensis aetheroleum partim mentholum depletum (mint oil, partly dementholised).

CAS — 68917-18-0 (commint oil).

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

Mentha oil is in *Jpn.*

Ph. Eur. 8: (Mint Oil, Partly Dementholised; Menthae Arvensis Aetheroleum Partim Mentholum Depletum; Dementholised Mint Oil BP 2014). The essential oil obtained by steam distillation from the fresh, flowering aerial parts, recently gathered from *Mentha canadensis* (*M. arvensis* var. *glabrata*; *M. arvensis* var. *piperascens*) followed by partial separation of menthol by crystallisation. A colourless or pale yellow to greenish-yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Dementholised mint oil is used as a flavour. *Mentha arvensis* is used in herbal medicine as a febrifuge and for rheumatic disorders. Cornmint oil, obtained from *M. arvensis*, is used in aromatherapy as an adulterant or substitute for peppermint oil. Peppermint oil (p. 1877.1) and spearmint oil (p. 2621.2) are used as carminatives and flavours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Japol; ***Ger.***: Japanol; JHP Rodler; Novopin MIG neu; Retterspitz Muskel- und Nervenol; ***Pol.***: Migrenol†; ***Swed.***: Japol.

Multi-ingredient Preparations. ***Austral.***: Tiger Balm Oil; Tiger Balm Red; Tiger Balm White; ***Austria***: Parodontax†; ***Canad.***: Tiger Balm Arthritis Rub; Tiger Balm Patch Warm; ***Chile***: Astrijesan; Calmatol; ***Fr.***: Esculape†; Tigre de Chine; ***Ger.***: Dreierlei; ***Hung.***: Salonpas Liniment; Tiger Balm Red; Tiger Balm White; ***Irl.***: Olbas; Tiger Balm Red; Tiger Balm White; ***Israel***: Tiger Balm Red; Tiger Balm White; ***Ital.***: Broncosedina; Listerine Fresh Citrus; Listerine Tartar Control; Venalta; ***Malaysia***: Eucarbon; ***Neth.***: Olbas†; ***Pol.***: Argol Essenza Balsamica; Milocardin; Mucosit; Rapacholin C; Rapacholin Forte; Rhin-Bac; Salviasept; ***Switz.***: Baume du Tigre blanc; Baume du Tigre rouge; DemoPectol; Kernosan Eau Dentifrice†; Malveol; Novital; Odontal; Onguent nasal Ruedi; Phlogantin†; Pommade nasale de Nager†; Pommade nasale de Ruedi†; Radix†; Tyrothricin†; Unathene†; ***Turk.***: Sandolin†; ***UK***: Olbas for Children; Olbas; Sinose; ***Ukr.***: Phytolysin Plus (Фитолизин Плюс); ***USA***: Tiger Balm.

Miracle Fruit

Fruta milagrosa; Магический Фрукт.

NOTE. The name Miracle Fruit has also been applied to *Gymnema sylvestre* and *Thaumatococcus daniellii*.

Profile

Miracle fruit is the fruit of *Synsepalum dulcificum* (*Richardella dulcifica*) (Sapotaceae). It contains a glycoprotein 'miraculin' with no apparent taste of its own but which is able to make sour substances taste sweet and to improve the flavour of foods. Its activity is reduced by heating.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ukr.***: Lipomin (Липомин); Liponorm (Липонорм).

Mistletoe

European Mistletoe; Gui; Mistelkraut; Muérdago; Tallo de Muérdago; Visci Caulis; Visci herba; Viscum; Viscum Album; Omela.

ATC Herb — HC02KA5003 (Viscum album: extract); HL01CW5001 (Viscum album: herb).

UNII — E6839Q6DO1 (Viscum album); P83EQ521R3 (Viscum album fruit); BK9092J5MP (Viscum album fruiting top).

Pharmacopoeias. In *Ger.*

Uses and Administration

Mistletoe is the dried, evergreen, dioecious semi-parasite, *Viscum album* (Loranthaceae), which grows on the branches of deciduous trees, chiefly apple, poplar, and plum. It occurs as a mixture of broken stems and leaves and occasional fruits. Mistletoe has a vasodilator action and has been used in herbal preparations for hypertension and cardiovascular disorders although its activity when taken orally is questionable. It has also been used in nervous disorders.

Mistletoe contains lectins with cytotoxic and immunomodulatory actions *in vitro* and preparations have been given by injection in neoplastic disease.

Homoeopathy

Mistletoe has been used in homoeopathic medicine under the following names: Viscum; Viscum album; Vis. alb.

Malignant neoplasms. Reviews[1-3] of the use of mistletoe for the treatment of malignant neoplasms revealed that studies have been of variable quality, and have produced conflicting results; it has been suggested that the more rigorous studies do not show benefit.[3] A systematic review of 21 randomised controlled studies found major methodological flaws in most of the studies and concluded that there was insufficient evidence to provide guidelines for the use of mistletoe extracts in oncology.

1. Mansky PJ. Mistletoe and cancer: controversies and perspectives. *Semin Oncol* 2002; **29**: 589–94.
2. Kienle GS, *et al.* Mistletoe in cancer—a systematic review on controlled clinical trials. *Eur J Med Res* 2003; **8**: 109–19.
3. Ernst E, *et al.* Mistletoe for cancer? A systematic review of randomised clinical trials. *Int J Cancer* 2003; **107**: 262–7.
4. Horneber M, *et al.* Mistletoe therapy in oncology. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 03/06/08).

Adverse Effects

Ingestion of the berries and other parts of mistletoe has been reported to cause nausea, vomiting, diarrhoea, and bradycardia.

A review of mistletoe.[1] There are about 1300 species of mistletoe representing 36 genera of the Loranthaceae, and what is called the "common mistletoe" varies from country to country: in Europe the term describes *Viscum album* while in the USA it describes *Phoradendron flavescens*. The toxicity of aqueous extracts of mistletoe has been found to depend upon the nature of the host plant. Three classes of cytotoxic compounds are present in the leaves and stems of *V. album* although the berries are generally considered to be the most toxic part of the plant. These are alkaloids, viscotoxins, and lectins. The viscotoxins have been shown to cause hypotension, bradycardia, arterial vasoconstriction, and a negative inotropic effect, and may act as acetylcholine agonists. The lectins show toxic effects in *animals* similar to those seen with ricin.

There have been reports of hepatitis after the ingestion of herbal remedies containing mistletoe.[2,3] Severe delayed hypersensitivity has been reported[4] in a patient given intravenous chemotherapy for breast cancer concurrently with subcutaneous injections of a mistletoe extract. It was thought that mistletoe had stimulated the reaction to methotrexate and gemcitabine.

1. Anderson LA, Phillipson JD. Mistletoe—the magic herb. *Pharm J* 1982; **229**: 437–9.
2. Harvey J, Colin-Jones DG. Mistletoe hepatitis. *BMJ* 1981; **282**: 186–7.
3. Weeks GR, Proper JS. Herbal medicines—gaps in our knowledge. *Aust J Hosp Pharm* 1989; **19**: 155–7.
4. Shaw HS, *et al.* Delayed-type hypersensitivity reaction with Iscador M given in combination with cytotoxic chemotherapy. *J Clin Oncol* 2004; **22**: 4432–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Eurixor; Helixor; Iscador; Isorel; Lektinol; ***Cz.***: Nat Jmeli†; ***Ger.***: Abnobaviscum; Cefalektin†; Eurixor†; Helixor; Iscador; Iscucin; Lektinol; Mistel Curarina; Mistel-Krautertabletten; Misteltropfen Hofmanns; Salus Mistel-Tropfen; Viscysat†; ***Switz.***: Helixor; Iscador.

Multi-ingredient Preparations. ***Austral.***: Calmo†; ***Austria***: Rutiviscal; Wechseltee St Severin; ***Canad.***: Herbal Insomnia†; Salusan†; ***Cz.***: Alvisan Neo; Hypotonicka†; ***Ger.***: Antihypertonicum S; Ilja Rogoff; Iscador c Arg; Iscador c Cu; Iscador c Hg; ***Hung.***: Sam-Ginseng Royal; Sanhelios 333; ***Pol.***: Cravisol; Doppelherz Energovital Tonik†; Venoforton; ***Rus.***: Doppelherz Energotonik (Доппельгерц Энерготоник); Herbion Drops for the Heart (Гербион Сердечные Капли)†; ***Ukr.***: Herbion Drops for Heart (Гербион Сердечные Капли)†.

Homoeopathic Preparations. ***Austria***: Cefavora; Homviotensin; Veratrum Med Complex; ***Canad.***: Ateria-Heel†; Candida Yeast Relief; Ginkgo-Comp†; Homeo-Form C†; HPB Complex†; Hylands LCQ; Hylands Leg Cramps; Leg Cramps with Quinine; Urarthone†; Visceel†; ***Fr.***: Hypophysis Complexe No 31†; Kalium Iodatum Complexe No 84†; L 25; Poconeol no 43; Poconeol no 5; Poconeol no 65†; Tarentula Complexe No 71; Urarthone; ***Ger.***: Antihypertonicum N†; Antihypertonicum-Tropfen N†; Arthrocalman; Cefavora†; Derivatio H; Derivatio; Evisco Mistel Urtinktur; Evisco Misteltropfen N; Flenin; Hewerheum N†; Homviotensin; Juv 110; Kattwicor; Lachemistol; Lowe-Komplex Nr 3; Lymphdiaral; Miburell; Panalgan; Phyto-C; Plantacard N; Plenosol; RauwolfiaViscomp; Roth's Rotacard; Uwobletten Arteriosklerose-Complex†; Vertizin; Viscum album H†; Viscum Album HM†; Viscum-Entoxin N; ***Neth.***: Actelite; Chavita 6; Co-Hypert; ***Rus.***: Crataegus-Plus (Крателгус-Плюс); ***Ukr.***: Cefavora (Цефавора); Homviotensin (Хомвиотензин).

Mitratapide *(USAN, rINN)*

Mitratapid; Mitratapida; Mitratapidum; R-103757; Митрата-пид.

2-[(2*R*)-Butan-2-yl]-4-(4-{4-[4-{{(2*S*,4*R*)-2-(4-chlorophenyl)-2-[(4-methyl-4*H*-1,2,4-triazol-3-ylsulfanyl)methyl]-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

$C_{36}H_{41}ClN_8O_4S$=717.3

CAS — 179602-65-4.

ATC Vet — QA08AB90.

UNII — FVW7175XP4.

Profile

Mitratapide is an inhibitor of the microsomal triglyceride transfer protein. It is used in veterinary medicine as an aid to management of obesity in *dogs*.

Monoclonal Antibodies

Nomenclature

The official nomenclature of monoclonal antibodies discussed here is intended to identify the specific therapeutic target of the antibody and the origin of its immunoglobulin sequence, which is discussed further under Uses and Administration, below.

The prefix of a name is unique to each specific monoclonal antibody, but names for all monoclonal antibodies have the suffix **-mab**.

The prefix of a name is followed by a substem that gives an indication of the pharmacological category or therapeutic target of the monoclonal antibody, for example:

- **-b(a)-** bacterial
- **-c(i)-** cardiovascular
- **-f(u)-** fungal
- **-k(i)-** interleukin
- **-l(i)-** immunomodulator
- **-s(o)-** bone
- **-t(u)-** tumour
- **-v(i)-** viral

Another substem indicating the genetic origin of the immunoglobulin sequence of the monoclonal antibody follows the therapeutic substem and immediately precedes the suffix, for example:

- **-o-** murine
- **-xi-** chimeric
- **-zu-** humanised
- **-u-** fully human

Examples of monoclonal antibodies named under this system are:

- elsilimomab (p. 2534.1) – immunomodulator, murine
- tositumomab (p. 874.2) – antitumour, murine
- abciximab (p. 1281.1) – cardiovascular, chimeric
- infliximab (p. 74.2) – immunomodulator, chimeric
- palivizumab (p. 2415.2) – RSV antibody, humanised
- tocilizumab (p. 77.3) – immunomodulator, humanised
- trastuzumab (p. 875.3) – antitumour, humanised
- canakinumab (p. 34.2) – interleukin-1β inhibitor, human
- denosumab (p. 1182.1) – bone disorders, human
- panitumumab (p. 843.1) – antitumour, human

The system for indicating therapeutic category is not, however, completely reliable, especially for a monoclonal antibody that has more than one use, or one that is used for an indication that was not its original intended target. Names of earlier monoclonal antibodies also include therapeutic substems that have been excluded from later nomenclature lists, for example edrecolomab (p. 786.1) used for colorectal cancer and oregovomab (p. 838.1) investigated for ovarian cancer.

If a monoclonal antibody is radiolabelled or conjugated to another substance such as a toxin or antineoplastic drug, this should be reflected by use of a second word to form the name (e.g. gemtuzumab ozogamicin, p. 802.2). Likewise, pegylated monoclonal antibodies are named using a second word 'pegol' (e.g. certolizumab pegol, p. 39.1) or related designation, although the prefix **peg-** has also been used.

References.

1. WHO. *General policies for monoclonal antibodies.* Geneva: WHO, 2009. Available at: http://www.who.int/medicines/services/inn/Generalpoliciesformonoclonalantibodies2009.pdf (accessed 06/04/10)
2. AMA (USAN). Monoclonal antibodies. Available at: http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies_prim.html (accessed 06/04/10)

Uses and Administration

In order to understand the structure and function of monoclonal antibodies and the rationale for their use, it is necessary to understand the basic structure of antibodies in general.

Antibodies (immunoglobulins) are high-molecular-weight glycoproteins produced by B lymphocytes in response to antigenic stimulation. They are made up of 4 amino acid chains comprising two heavy chains and two light chains arranged in a Y-shape. The heavy chains (Fc domain; complement binding) constitute the constant region of the molecule and determine its effector function—for example, whether it binds to Fc receptors on immune cells or activates the complement cascade; the amino acid sequence of the Fc domain is identical for all antibodies within a class (e.g. IgA, IgD, IgE, IgG, IgM). The light chains (Fab domain; fragment antigen binding) constitute the variable region of the molecule and form the antigen binding site; specific amino acid sequences (the complementarity-determining region) determine the ability of the antibody to bind to the epitope (the antigenic determinant) of the target molecule and the degree of binding. There may be several different epitopes on one antigen and a usual antibody response *in vivo* will therefore produce polyclonal antibodies (e.g. antisera, see p. 2373.1). **Monoclonal antibodies**, on the other hand, are identical antibodies produced by a single clone of B lymphocytes that will bind only to a specific epitope on the target antigen. Monoclonal antibodies interact with, and influence, the function of target molecules through binding, blocking, or signalling, depending on the Fab region of the antibody.

Monoclonal antibodies were first produced by hybridoma technology, which was described by Köhler and Milstein in 1975, although the first therapeutic monoclonal antibody for human use, muromonab-CD3 (p. 1960.1), was not developed until 1986. In the original hybridoma technique, mice were immunised with a specific antigen to stimulate B-lymphocytes to produce antibodies against that antigen. The B-lymphocytes were extracted from the mice spleen cells and fused with cultured tumour cells to form immortal hybrid cell lines (hybridomas) that were then screened for monoclonal antibodies of interest. In this way, identical antibodies could be produced in large quantities over a prolonged period. Unfortunately, murine monoclonal antibodies can be unreliable, have short half-lives and limited efficacy, and generate production of antibodies with the potential for serious adverse effects (see p. 2562.2). Using recombinant DNA technology, chimeric monoclonal antibodies can be produced in which the Fab region of the mouse-derived antibody is combined with the Fc region of a human antibody to try and improve the safety profile (e.g. infliximab, p. 74.2 and rituximab, p. 852.1). The total human genetic component of chimeric monoclonal antibodies is between 60 and 90%, and while safer than murine monoclonal antibodies, there are still problems with adverse effects. Further developments in genetic engineering have produced humanised antibodies in which the amino acid sequences of the complementarity-determining region from the mouse Fab region are incorporated into the Fab region of a human antibody to increase the total human genetic component to around 90 to 95% (e.g. bevacizumab, p. 747.1 and trastuzumab, p. 875.3). Fully human monoclonal antibodies with 100% human genetic composition (e.g. adalimumab, p. 17.2 and panitumumab, p. 843.1) can now be developed through new biotechnologies such as antibody phage display in which human antibody sequences are cloned or designed, or the use of transgenic mice carrying human antibody genes. Other developments include modification of monoclonal antibodies to produce a fragment that lacks the Fc region (e.g. abciximab, p. 1281.1 and ranibizumab, p. 2602.1). Monoclonal antibodies can also be attached to another drug such as a cytotoxic drug (e.g. gemtuzumab ozogamicin, p. 802.2), a radioactive isotope (e.g. ibritumomab tiuxetan chelated with indium-111 or yttrium-90, see p. 804.3), or a toxin (e.g. zolimomab aritox); these are called conjugated monoclonal antibodies, whereas unconjugated monoclonal antibodies are referred to as 'naked'. The nomenclature of monoclonal antibodies reflects the genetic origin of the immunoglobulin sequence of monoclonal antibodies and is discussed above, under Nomenclature.

Monoclonal antibodies have been produced for a variety of different uses, including diagnostics, therapeutics, veterinary practice, food industry, agriculture, and vaccine preparation. Therapeutic uses include neovascular (wet) age-related macular degeneration, allergic asthma, bacterial and viral infections, cardiovascular disorders, immunosuppression in transplant recipients, inflammatory bowel disease, inflammatory joint disorders, malignant neoplasms, multiple sclerosis, paroxysmal nocturnal haemoglobinuria, and plaque psoriasis.

References.

1. Mascelli MA, *et al.* Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. *J Clin Pharmacol* 2007; 47: 553–65.
2. Anonymous. Understanding monoclonal antibodies. *Drug Ther Bull* 2007; 45: 55–6.
3. Martin-Mateos MA. Monoclonal antibodies in pediatrics: use in prevention and treatment. *Allergol Immunopathol (Madr)* 2007; 35: 145–50.
4. Samaranayake H, *et al.* Challenges in monoclonal antibody-based therapies. *Ann Med* 2009; 41: 322–31.
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6. Wang DD, *et al.* Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J Clin Pharmacol* 2009; 49: 1012–24.
7. Keizer RJ, *et al.* Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet* 2010; 49: 493–507.

Cardiovascular disorders. Abciximab (p. 1281.1) is a chimeric monoclonal antibody Fab fragment that targets the glycoprotein IIb/IIIa-receptor on the surface of human platelets and prevents the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa-receptor sites on activated platelets. Abciximab thus inhibits platelet aggregation and is used as an adjunct to heparin and aspirin therapy in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p. 1259.2).

Cryopyrin-associated periodic syndromes. Canakinumab (p. 34.2) is a human monoclonal antibody that binds to interleukin-1β and blocks its interaction with interleukin-1 receptors, thus preventing activation of the interleukin-1β-induced gene and the production of inflammatory mediators. It is used in the treatment of cryopyrin-associated periodic syndromes including familial cold auto-inflammatory syndrome and Muckle-Wells syndrome, which are rare inherited auto-inflammatory disorders.

Dermatological disorders. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of plaque psoriasis (p. 1688.1), and examples of monoclonal TNF antibodies used in clinical practice include the chimeric antibody infliximab (p. 74.2) and the human antibody adalimumab (p. 17.2). Ustekinumab (p. 1728.2) is a human monoclonal antibody that binds to interleukins 12 and 23 and is also used in the treatment of plaque psoriasis. Efalizumab (p. 1702.2) is a humanised monoclonal antibody that binds to CD11a on leucocytes to inhibit the activation of T-lymphocytes. It has been used to treat plaque psoriasis but was withdrawn from the market in the USA and Europe because of reports of progressive multifocal leukoencephalopathy.

Inflammatory bowel disease. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of inflammatory bowel diseases (p. 1808.3) such as Crohn's disease and ulcerative colitis, and examples of monoclonal TNF antibodies used in clinical practice include the chimeric antibody infliximab (p. 74.2) and the human antibody adalimumab (p. 17.2). Certolizumab pegol (p. 39.1) is a pegylated humanised TNF antibody fragment used in the treatment of Crohn's disease.

Inflammatory joint disorders. Monoclonal antibodies that target the inflammatory cytokine tumour necrosis factor (TNF) are used in the treatment of inflammatory joint disorders such as rheumatoid arthritis (p. 13.2), juvenile idiopathic arthritis (p. 12.1), psoriatic arthritis (see under Spondyloarthropathies, p. 14.3), and ankylosing spondylitis (see under Spondyloarthropathies, p. 14.3). Examples of monoclonal TNF antibodies used in clinical practice for various arthritides include the chimeric antibody infliximab (p. 74.2), the humanised antibody tocilizumab (p. 77.3), the pegylated humanised TNF antibody fragment certolizumab pegol (p. 39.1), and the human antibodies adalimumab (p. 17.2) and golimumab (p. 66.3). Rituximab (p. 852.1) is a chimeric anti-CD20 monoclonal antibody used as adjunctive treatment for rheumatoid arthritis.

Lymphoproliferative disorders. Tocilizumab (p. 77.3) is a humanised monoclonal antibody that specifically targets both soluble and membrane-bound interleukin-6 receptors thereby inhibiting interleukin-6 signalling. It is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder.

Malignant neoplasms. Tumour cells express several different antigens each of which is a potential target for development of a specific monoclonal antibody that can generate immune responses with consequential direct or indirect anti-tumour effects. Monoclonal antibodies can also be conjugated with antineoplastic drugs, toxins, or radioisotopes and specifically targeted to tumour receptors in order to avoid damaging healthy tissue.

Trastuzumab (p. 875.3) is a humanised monoclonal antibody directed against the cell surface protein produced by the human epidermal growth receptor 2 (HER2) gene. HER2 protein is overexpressed in some tumours, and trastuzumab is used in the treatment of breast cancer (p. 702.1). Other monoclonal antibodies that bind to the epidermal growth factor receptor include the chimeric antibody cetuximab (p. 762.3) used in the treatment of

metastatic colorectal cancer (p. 706.3) and cancers of the head and neck (p. 708.1), the humanised antibody nimotuzumab (p. 836.3) used in the treatment of glioma (see under Malignant Neoplasms of the Brain, p. 701.2) and cancers of the head and neck, and the human antibody panitumumab (p. 843.1) used in the treatment of metastatic colorectal cancer in patients with disease progression after other therapies.

Bevacizumab (p. 747.1) is a humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis. It is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer, with paclitaxel in the treatment of metastatic breast cancer, with platinum-based chemotherapy in the treatment of non-small cell lung cancer (p. 710.2), and with interferon alfa in the treatment of renal cell carcinoma (p. 708.3). Bevacizumab is also used for progressive glioblastoma (see under Malignant Neoplasms of the Brain, p. 701.2).

Edrecolomab (p. 786.1) is a murine monoclonal antibody directed at epithelial cell surface glycoproteins that has been used as adjuvant therapy after surgery for colorectal cancer.

Rituximab (p. 852.1) is a chimeric monoclonal antibody targeted to the CD20 antigen of B lymphocytes that is used in the treatment of non-Hodgkin's lymphoma (p. 696.3). Alemtuzumab (p. 737.1) is a humanised monoclonal antibody directed against the CD52 antigen of lymphocytes that is used in the treatment of chronic lymphocytic leukaemia (p. 693.3).

Catumaxomab (p. 762.2) is a rat-mouse hybrid monoclonal antibody used for the treatment of malignant ascites (see under Malignant Effusions, p. 700.1) in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

Gemtuzumab ozogamicin (p. 802.2) is a humanised monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. It is used for the second-line treatment of CD33-positive acute myeloid leukaemia (p. 693.1) in elderly patients unable to tolerate conventional chemotherapy.

Ibritumomab is a murine monoclonal antibody targeted to the CD20 antigen of B lymphocytes that is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. In the management of non-Hodgkin's lymphoma, ibritumomab tiuxetan (p. 804.3) is chelated with indium-111 and used for imaging, whereas it is chelated with yttrium-90 and used for radio-immunotherapy. Likewise, tositumomab (p. 874.2) is a murine monoclonal antibody also targeted to the CD20 antigen and radiolabelled with iodine-131 for use in the treatment of non-Hodgkin's lymphoma.

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Multiple sclerosis. Natalizumab (p. 2567.2) is a humanised monoclonal antibody that binds to α4β1-integrin, which is highly expressed on the surface of all leucocytes, with the exception of neutrophils, thereby preventing transmigration of mononuclear leucocytes across the endothelium into inflamed parenchymal tissue. It has been found to decrease the frequency of exacerbations in relapsing-remitting multiple sclerosis (p. 996.3) but it has been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore restricted. Alemtuzumab (p. 737.1) is also licensed for use in the treatment of multiple sclerosis; when compared with interferon beta-1a, it significantly reduced the rate of relapse in previously untreated patients with relapsing-remitting multiple sclerosis and also in patients who had relapsed after first-line treatment. Other monoclonal antibodies are being investigated for the treatment of multiple sclerosis and include daclizumab (p. 1957.1) and rituximab (p. 852.1).

References:
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Ocular disorders. Ranibizumab (p. 2602.1) is a humanised monoclonal antibody Fab fragment that binds to and inhibits vascular endothelial growth factor A (VEGF-A), thereby preventing its action in endothelial cell proliferation and neovascularisation, as well as vascular leakage. Ranibizumab is used for the treatment of neovascular (wet) age-related macular degeneration (p. 880.2). Bevacizumab (p. 747.1) is a related humanised monoclonal antibody also used to treat this condition, although it is unlicensed for such use and has been associated with adverse effects.

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Organ and tissue transplantation. Muromonab-CD3 (p. 1960.1) is a murine monoclonal antibody that targets the T3 (CD3) antigen of human T-lymphocytes, which is essential to antigen recognition and response. Binding to T-cells activates complement, which depletes T-cell populations. Muromonab-CD3 is used in the treatment of acute allograft rejection in organ transplant recipients (see p. 1932.2).

Monoclonal antibodies that target CD25, a subunit of the interleukin-2 receptor, are also used as immunosuppressants in transplantation. The binding of interleukin-2 to the T-cell is blocked by the monoclonal antibody, and thus inhibits T-cell activation. Basiliximab (p. 1944.1) is a chimeric monoclonal antibody that functions as an interleukin-2 receptor antagonist. It used in combined immunosuppressive regimens for the prevention of acute graft rejection following renal transplantation (p. 1935.2). Daclizumab (p. 1957.1) is a humanised monoclonal antibody used similarly.

Paroxysmal nocturnal haemoglobinuria. Eculizumab (p. 2499.1) is a humanised monoclonal antibody that acts as a complement blocker by inhibiting terminal complement activation at the C5 protein. It is used to reduce haemolysis in patients with paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia (p. 1122.2).

Respiratory disorders. Omalizumab (p. 1216.3) is a humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and reduces the amount of free IgE available to trigger the allergic cascade. It is used in the prophylactic management of allergic asthma (p. 1195.2).

Palivizumab (p. 2415.2) is a humanised monoclonal antibody to respiratory syncytial virus (RSV) for the passive immunisation of infants against RSV infection (p. 961.3).

1. Schachter EN, Neuman T. The use of monoclonal antibodies and related agents in the treatment of respiratory disease. *Drugs Today* 2009; 45: 533–48.

Adverse Effects and Precautions

Early murine monoclonal antibodies were associated with serious immune-mediated adverse effects, and although later development of chimeric, humanised, and fully human monoclonal antibodies (described under Uses and Administration, p. 2561.1) has improved their safety profile, these substances can still present problems due to their potent interaction with the immune system. Patients with significantly compromised immune systems should not generally be given monoclonal antibodies.

Serious hypersensitivity reactions, including anaphylaxis, can occur with monoclonal antibodies, although the mechanism of action is not clear in many cases since the production of specific immunoglobulin E has been rarely shown. Infusion reactions associated with a cytokine release syndrome commonly occur at the start of a monoclonal antibody infusion. Injection site reactions have also been reported. Antibodies to the monoclonal antibody develop in some patients, although it is not entirely clear how this affects safety and efficacy.

Monoclonal antibodies have been associated with an increased incidence of serious infections and should therefore be given with caution to patients with active infections, a history of recurring infections, or underlying conditions that may predispose them to developing infections. Treatment should not be started or continued in patients with severe infections that require treatment. There have been cases of progressive multifocal leukoencephalopathy (PML) reported with some monoclonal antibodies such as efalizumab (p. 1702.2), natalizumab (p. 2568.1), and rituximab (p. 854.1).

The adverse effects of monoclonal antibodies are discussed in greater detail in specific monographs.

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Monoctanoin *(BAN, USAN)*

Glycerol Monocaprylate; Glyceroli Monocaprylas; Glyceroimonocaprylat; Glyceryl Caprylate; Glyceryl Mono-octanoate; Monocaprylin; Monoctanoina; Monooctanoin; Monooctanoin.

CAS — 26402-26-6 (glyceryl mono-octanoate).

UNII — VFU0OU98LO (monoctanoin); TM2TZD4G4A (glyceryl mono-octanoate); 197M6VFC1W (glyceryl mono-decanoate); SA9937IP23 (glyceryl di-octanoate).

NOTE. Monoctanoin (*BAN, USAN*) is a semisynthetic mixture containing 80 to 85% of glyceryl mono-octanoate ($C_{11}H_{22}O_4$ = 218.3), 10 to 15% of glyceryl mono-decanoate (glyceryl caprate) ($C_{13}H_{26}O_4$ = 246.3) and glyceryl di-octanoate (glyceryl dicaprylate) ($C_{19}H_{36}O_5$ = 344.5), and a maximum of 2.5% of free glycerol ($C_3H_8O_3$ = 92.09).

Pharmacopoeias. *Eur.* (see p. vii) includes Glycerol Monocaprylate.

Ph. Eur. 8: (Glycerol Monocaprylate). A mixture of monoacylglycerols, mainly mono-*O*-octanoylglycerol, (glyceryl mono-octanoate; glyceryl caprylate), containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol with octanoic acid, followed by a distillation step in the case of glycerol monocaprylate (type II). Content of glycerol monocaprylate (type I): monoacylglycerols: 45 to 75%; diacylglycerols: 20 to 50%; triacylglycerols: maximum 10%. Content of glycerol monocaprylate (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

Monoctanoin is a mixture of glyceryl esters (p. 2186.3) containing mainly glyceryl monocaprylate. It has been given by continuous perfusion through a catheter inserted directly into the common bile duct to dissolve cholesterol gallstones (p. 2639.1) retained after cholecystectomy. Similar mixtures, known as glyceryl monocaprylates, are used as solvents and emulsifiers in pharmaceutical preparations.

Monoethanolamine

Colamine; Моноэтаноламин.

2-Hydroxyethylamine; 2-Aminoethanol.

C_2H_7NO=61.08

CAS — 141-43-5.

Pharmacopoeias. In *Br.* Also in *USNF.*

BP 2014: (Ethanolamine). A clear, colourless, or pale yellow liquid with a slight odour. It is alkaline to litmus. Miscible with water and with alcohol; slightly soluble in ether.

USNF 31: (Monoethanolamine). A clear, colourless, moderately viscous liquid having a distinctly ammoniacal odour. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerol; immiscible with ether, with petroleum spirit, and with fixed oils, although it dissolves many essential oils. Store in airtight containers. Protect from light.

Monoethanolamine Oleate *(rINN)*

Ethanolamine Oleate (USAN); Monoetanolamina, oleato de; Monoéthanolamine, Oléate de; Monoethanolamini Oleas; Oleato de monoetanolamina; Моноэтаноламина Олеат.

2-Hydroxyethylamine compound with oleic acid; 2-Aminoethanol compound with oleic acid.

$C_2H_7NO.C_{18}H_{34}O_2$=343.6

CAS — 2272-11-9.

ATC — C05BB01.
ATC Vet — QC05BB01.
UNII — U4RY8MRX7C.

Uses and Administration

Monoethanolamine oleate is used as a sclerosant in the treatment of varicose veins and oesophageal varices. For sclerotherapy of varicose veins, 2 to 5 mL of a 5% solution of monoethanolamine oleate is injected slowly into empty isolated sections of vein, divided between 3 or 4 sites. Injection into full veins is also possible. For sclerotherapy of oesophageal varices, the dose is 1.5 to 5 mL of a 5% solution per varix to a maximum total dose of 20 mL per treatment session. Treatment may be given in the initial management of bleeding varices, then repeated at intervals until the varices are occluded.

Variceal haemorrhage. Portal hypertension may occur in many conditions that affect the liver, and leads to the development of collateral channels linking the portal and systemic circulations. Enlargement of such blood vessels beneath the oesophageal and gastric mucosa produces varices which have about a 30% risk of rupture and bleeding. Oesophageal varices are more often a cause of haemorrhage than gastric varices. Capillaries and veins in the gastric mucosa may also become swollen, a condition known as portal hypertensive gastropathy, and clinically important bleeding may occur in severe cases.

Variceal haemorrhage is usually severe, with mortality as high as 50% for the initial episode; the recurrence rate may be as high as 100% in patients who survive without treatment. Bleeding may stop spontaneously, but in those who continue to bleed, control of haemorrhage is difficult and patients should be referred to a centre with appropriate specialist facilities. Treatment to stabilise the patient may be necessary before they can be safely transferred.

Acute management. Initial treatment is supportive and requires measures to prevent aspiration and maintain a clear airway, and volume replacement with colloid and blood. Emergency endoscopy should be performed to establish the site of haemorrhage and exclude non-variceal sources of bleeding. The choice of treatment depends on the site of haemorrhage.[1-11] ***Endoscopic methods*** have been favoured for initial management. Injection sclerotherapy or banding ligation are used for bleeding oesophageal varices but the optimum management of bleeding gastric varices remains to be defined; the value of injection sclerotherapy varies with their location. Intravariceal injection of bovine or human thrombin, or cyanoacrylate tissue adhesives, has been used in gastric varices. Where the source of haemorrhage is non-variceal and due to gastropathy, portal decompressive surgery is effective, although it is associated with a high incidence of encephalopathy in cirrhotic patients. Small studies have shown propranolol to be effective in arresting haemorrhage.[12]

Injection sclerotherapy for variceal haemorrhage may be performed during the emergency endoscopy procedure. Intravariceal injection, paravariceal injection, or a combination of the two have been used. The most widely used sclerosants are monoethanolamine oleate and sodium tetradecyl sulfate for intravariceal injection and lauromacrogol 400 for paravariceal injection. Sclerotherapy controls bleeding in up to 95% of cases. Ulceration and stricture formation occur frequently following injection sclerotherapy.

An alternative technique is ***endoscopic banding ligation***, where elastic bands are placed around the varices. The tissue subsequently necroses to leave a superficial ulcer. This technique is more successful than injection sclerotherapy, but may be more difficult to perform if active bleeding is occurring. Procedures may be repeated if bleeding continues or restarts.

Where endoscopy is unavailable, drug therapy or balloon tamponade may be used until the patient can be transferred to a specialist centre. These techniques may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy[13] or endoscopy.[14]

Drug therapy is aimed at controlling portal venous pressure, although it is ineffective in massive haemorrhage and its effects cease once the drug is stopped. Two meta-analyses[13,15] have examined data from studies comparing drug therapy with endoscopic methods for the treatment of acute variceal bleeding. Sclerotherapy did not appear to be superior to vasoactive drugs as the first single treatment, and was associated with more frequent adverse effects.[13] Adjunctive drug therapy improved the efficacy of endoscopic therapy (injection sclerotherapy or banding ligation) compared with endoscopic methods alone, although overall mortality was not affected; severe adverse effects were similar in both groups.[15]

Drugs used include vasopressin and its analogue terlipressin and, more recently, somatostatin and its analogue octreotide. Vasopressin controls haemorrhage in about 50% of patients. It is given by continuous intravenous infusion, with glyceryl trinitrate, which counteracts the adverse cardiac effects of vasopressin, while potentiating its reduction of portal pressure. Terlipressin has the advantage of a longer therapeutic action, enabling bolus doses to be given. A comparison[16] of terlipressin and sclerotherapy found them to be equally effective for the control of acute variceal bleeding. A systematic review[17] of studies comparing terlipressin with placebo, or other drugs or interventions, also gave favourable results. However, somatostatin,[2] and particularly octreotide,[2,18,19] which may be given by bolus injection, are now generally preferred as they are thought to have similar efficacy to vasopressin but fewer adverse effects. A systematic review[20] of studies comparing somatostatin or its analogues octreotide and vapreotide with either placebo or no drug treatment suggested a small benefit in controlling bleeding; however, no mortality benefit has yet been shown. Clinical studies with recombinant factor VIIa to control acute variceal bleeding have produced beneficial results.[14]

Balloon tamponade controls bleeding by direct pressure on the varices. Although it is a very effective means of controlling haemorrhage, there is a high incidence of rebleeding once pressure is removed and the incidence of complications is high. It is useful in cases of massive haemorrhage when drug therapy is ineffective and sclerotherapy is difficult.

Surgery, such as the formation of a shunt or oesophageal transection, may be necessary if the above measures fail to control the bleeding. However, such techniques have been associated with high mortality in some series. Formation of a transjugular intrahepatic portal-systemic shunt (TIPS) is now generally preferred.[4] It may be particularly useful in candidates for liver transplantation. Limited data suggest that the shunt may remain patent in the majority of patients for at least 3 years.[21]

Short-term ***antibacterial prophylaxis*** has been proposed[22] for cirrhotic patients with gastrointestinal bleeding, including variceal bleeding, because reduced rates of infection and improved short-term survival have been reported in a few studies, although there is no benefit on overall mortality.[23]

Long-term management. Once the acute bleeding has been controlled measures are needed to prevent rebleeding.[10,11] Endoscopic therapy is widely used, with injection sclerotherapy or banding ligation being repeated until the varices are obliterated. Banding ligation is now the treatment of choice; it eradicates varices in fewer treatment sessions than injection sclerotherapy and reduces the risk of ulceration and stricture formation.[24,25] Sucralfate has been given following sclerotherapy as it may reduce the frequency of stricture formation and reduce bleeding from treatment-related ulcers. It seems to have no influence on ulcer healing following banding ligation.[26] Some practitioners carry out regular endoscopic checks and repeat sclerotherapy or banding ligation when varices reappear, although this approach is no more effective in terms of improving survival than giving treatment once bleeding occurs. Drug therapy is an alternative to endoscopic methods.[27] Beta blockers (mainly propranolol) reduce the incidence of recurrent variceal bleeding and may improve survival.[25,28,29] A combination of nadolol with isosorbide mononitrate has been reported to reduce the risk of rebleeding more than repeated sclerotherapy, although there was no significant effect on mortality.[30] Drug therapy has also been used as an adjunct to endoscopic methods to control rebleeding in the period before variceal obliteration has occurred, or for long-term management following endoscopic therapy, although studies comparing endoscopic banding ligation with combination drug therapy have produced variable results.[31] However, results from a meta-analysis[32] of 23 studies found that a combination of drug and endoscopic therapy is better than either treatment alone in the prevention of overall and variceal rebleeding; this effect was the same with either endoscopic injection sclerotherapy or banding ligation. Long-term octreotide therapy following sclerotherapy has also been investigated and may reduce recurrent variceal bleeding.[33] Several studies[34-36] have compared TIPS with endoscopic treatment, but no clear benefit has been shown and there may be an increased risk of encephalopathy with the use of shunts. Surgery, including liver transplantation, should be considered in patients with recurrent life-threatening haemorrhage. Propranolol may also have a role in patients with portal hypertensive gastropathy. In a controlled study, propranolol reduced the incidence of recurrent bleeding from portal hypertensive gastropathy in patients with cirrhosis.[37]

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed, but should probably be given to patients with cirrhosis and varices thought to be at high risk of bleeding.[11] A reliable system that will identify those at high risk of haemorrhage has yet to be devised. The NIEC (North Italian Endoscopic Club) system is probably the best so far,[38,39] and is based on size of the varices, presence of red wale marks on the varices, and Child-Pugh class; amendments to improve the traditional index have been suggested.[39] Sclerotherapy had been considered as a method of prophylaxis, but its value has not been clearly established. Studies show that beta blockers decrease the incidence of a first bleed[29,40] and are probably the treatment of choice if prophylaxis is to be given. Banding ligation may be a suitable alternative for patients who are unable to take beta blockers.[41] Others consider banding ligation to be the standard therapy for prophylaxis.[9] A meta-analysis[42] of 9 randomised controlled studies concluded that variceal banding ligation was superior to beta blockers in preventing a first variceal bleed, whereas a systematic review[43] of 16 randomised controlled studies found both treatments to be effective and suggested that the estimated effect of banding ligation in some studies may be biased and was associated with shorter duration of follow-up.

It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought, and isosorbide mononitrate[9,44,45] (as adjunctive therapy with a beta blocker) and clonidine[46] have been investigated for the prophylaxis of a first bleed and prevention of recurrent haemorrhage in patients with portal hypertension.

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Varicose veins. Varicose veins are tortuous, protruding veins in the legs, that occur when weak vein walls and valve incompetence result in venous reflux and dilatation. Symptoms associated with varicose veins include heaviness, tension, aching, and itching of the legs. Complications include oedema, thrombophlebitis, deep venous thrombosis, lipodermatosclerosis, and venous ulceration. Risk factors for varicose veins include increasing age, pregnancy, and occupations that involve prolonged standing.[1]

The management of varicose veins has been reviewed.[1-5] Conservative management using compression hosiery may be effective for relief of symptoms in some patients[4] but longer-term compliance is poor.[3,5] Surgery or sclerotherapy are other treatment options, depending on the veins affected. Surgical treatment, which is the gold standard for treatment of more severe varicose veins, may involve ligation of the affected vein, stripping of the affected stem vein, or avulsions of the varicosities.[3] In sclerotherapy, which may be the treatment of choice for thread veins,[2,4] a sclerosant is injected into the affected vein where it irritates and damages the lining of the vein causing local thrombosis, fibrosis, and stenosis. Detergent sclerosants include monoethanolamine oleate, sodium tetradecyl sulfate, lauromacrogol 400, and sodium morrhuate; osmotic sclerosants include hypertonic sodium chloride solutions, and hypertonic mixtures of sodium chloride and glucose; caustic sclerosants include chromated glycerol, and a mixture of iodine and sodium iodide. Graduated compression dressings are usually applied after sclerotherapy to minimise the time taken for the surrounding tissue to absorb the damaged segment of vein. Compression may also help to reduce complications of sclerotherapy including hyperpigmentation, oedema, aching, thrombophlebitis, and deep venous thrombosis. A systematic review[6] of randomised controlled studies of injection sclerotherapy failed to determine its place in the overall management of varicose veins, since the type of sclerosant, formulation, local pressure dressing, or degree and length of compression do not appear to have a significant effect on efficacy. However, the evidence supports its current place in practice, which is in the treatment of recurrent varicose veins following surgery, and thread veins. In another systematic review,[7] the use of surgery or sclerotherapy for the management of primary varicose veins was compared. There was a tendency for better early outcomes with sclerotherapy whereas surgery produced more long-term benefits. However, there was insufficient evidence to recommend the use of one form of treatment over the other, and the extent of the varicose veins ultimately governs the choice.

New methods of treatment being tried include foam sclerotherapy, in which a detergent-like sclerosant is mixed with air to create a foam,[2,4,5] ambulatory phlebectomy, endovenous laser therapy, and radiofrequency ablation.[3-5,8]

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Adverse Effects and Precautions

Monoethanolamine oleate is irritant to skin and mucous membranes. Local injection may cause sloughing, ulceration, and, in severe cases, necrosis. Pain may occur at the site of injection. Patients receiving treatment for oesophageal varices may develop pleural effusion or infiltration. Hypersensitivity reactions have been reported.

Sclerotherapy should not be used to treat varicose veins of the legs in patients unable to walk, with obese legs, with thrombosis or a tendency to thrombosis, or with acute phlebitis, marked arterial, cardiac, or renal disease, local or systemic infections, or uncontrolled metabolic disorders such as diabetes mellitus. Monoethanolamine oleate should not be used in patients taking oral contraceptives.

Effects on the kidneys. Acute renal failure, which cleared spontaneously within 3 weeks, occurred in 2 obese women given sclerosing injections of 15 to 20 mL of a solution containing monoethanolamine oleate 5% and benzyl alcohol 2%.[1]

1. Maling TJB, Cretney MJ. Ethanolamine oleate and acute renal failure. *N Z Med J* 1975; 82: 269–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Ethamolin; *Jpn*: Oldamin; *USA*: Ethamolin.

Pharmacopoeial Preparations
BP 2014: Ethanolamine Oleate Injection.

Motherwort

Agripalma; Agripaume, herbe de; Cardíaca; Cola de león; Herzgespannkraut; Hjärtstilla; Leonuri cardiacae herba; Leonuri Herba; Leonurus; Motherwort Herb; Nukula; Srdečníková nať; Sukatžolių žolė; Пустырник Сердечный.
ATC Herb — HN05CM5012 (Leonurus cardiaca: herb); HC01EB5016 (Leonurus cardiaca: herb).
UNII — 8NC0C2YXK0 (Leonurus cardiaca); U4SXX96Y4 (Leonurus cardiaca flowering top).

Pharmacopoeias. In *Eur.* (see p. vii). *Chin.* includes the fruit.

Ph. Eur. 8: (Motherwort). The whole or cut, dried, flowering aerial parts of *Leonurus cardiaca*. It contains not less than 0.2% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) calculated with reference to the dried drug. Protect from light.

Profile

Motherwort is given in herbal medicine for nervous and cardiac disorders; it is also used in products promoted for mild hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Biocarde; *Ger.*: Cimicifuga comp; Oxacant-sedativ; *Irl.*: Quiet Life; *Pol.*: Biovital N†; Gerovital Zdrovit; Klimax; Lumewal; Nervinolum; Nerwobonisol; Tabletki Tonizujace; Tabletki Uspokajajace; *Rus.*: Biovital (Биовиталл); Cedoflor (Седофлор); Kliophyt (Клиофит); Phyto Novo-Sed (Фито Ново-Седа); Sedativae Species No 2 (Седативный Сбор 2); Sedativae Species No 3 (Седативный Сбор 3); Valemidin (Валемидин); *Switz.*: Tisane pour le coeur et la circulation; *UK*: Menopause Relief; Modern Herbals Stress; Period Pain Relief; Prementaid; Quiet Life; SuNerven; Valerian Passiflora and Hops; Wellwoman; *Ukr.*: Cratal (Кратал); Flavia (Флавиа); Florised (Флорисед); Gerovital Dr. Theiss (Геровитал Др. Тайсс); Normoton (Нормотон); Sedafiton (Седафитон).

Homoeopathic Preparations. *Canad.*: Motherwort Combination 1†; Motherwort Combination 3†; *Fr.*: Hypophysis Complexe No 31†; *Ger.*: Arrhythmie-Gastreu N; Crataegus Herzcomplex; Hewethyreon N; *Neth.*: Nervival; *Rus.*: Valeriana-Plus (Валериана-Плюс).

Moxaverine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de moxaverina; Meteverine Hydrochloride; Moxaverina, hidrocloruro de; Moxaverine, Chlorhydrate de; Moxaverini Hydrochloridum; Моксаверина Гидрохлорид.
1-Benzyl-3-ethyl-6,7-dimethoxyisoquinoline hydrochloride.
$C_{20}H_{21}NO_3,HCl$=343.9
CAS — 10539-19-2 (moxaverine); 1163-37-7 (moxaverine hydrochloride).
ATC — A03AD30.
ATC Vet — QA03AD30.

Profile

Moxaverine has a similar structure to papaverine (p. 2362.2) and the hydrochloride has been given orally and by intravenous infusion in the treatment of vasospastic disorders and as an antispasmodic in gastrointestinal and biliary-tract spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Kollateral†.

Mozavaptan *(rINN)* ⊗

Manavaptan; Mozavaptán; Mozavaptane; Mozavaptanum; OPC-31260; Мозавантан.
N-(4-[[(5*RS*)-5-(Dimethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl]phenyl)-2-methylbenzamide.
$C_{27}H_{29}N_3O_2$=427.5
CAS — 137975-06-5.
UNII — 17QJ42922Y.

Profile

Mozavaptan is a selective vasopressin V_2-receptor antagonist used as the hydrochloride for the treatment of hyponatraemia in cancer-related syndrome of inappropriate antidiuretic hormone secretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Physuline.

Mucoproteose

Profile

Mucoproteose is a component of gastric mucus and has been included in some oral iron preparations to protect the gastrointestinal mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Tardyferon; *Belg.*: Tardyferon; *Cz.*: Tardyferon; *Ger.*: Tardyferon; *Hung.*: Tardyferon; *Pol.*: Tardyferon; *Port.*: Tardyferon; *Turk.*: Oroferon; Tardyferon; *Ukr.*: Tardyferon (Тардиферон).

Multi-ingredient Preparations. *Arg.*: Tardyferon; *Austria*: Tardyferon-Fol; *Cz.*: Tardyferon-Fol; *Fr.*: Tardyferon B_9; Tardyferon; *Ger.*: Tardyferon-Fol; *Hung.*: Tardyferon-Fol; *Pol.*: Tardyferon-Fol; *Port.*: Tardyferon-Fol; *Rus.*: Gyno-Tardyferon (Гино-тардиферон); *Switz.*: Gyno-Tardyferon; Tardyferon; *Turk.*: Gyno-Tardyferon; Gynoferon; *Ukr.*: Gyno-Tardyferon (Гино-Тардиферон).

Mulungu

Мулунгу.

Profile

The bark of the mulungu tree, *Erythrina verna* (*E. mulungu*) Fabaceae, has traditionally been used in South America as a sedative and as a hypotensive.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Calmapax; Passaneuro; Passaneuro; Ritmoneuran.

Mumps Skin Test Antigen

Parotiditis; prueba cutánea contra el antígeno de la.

Profile

Recovery from mumps produces skin hypersensitivity to mumps virus. Mumps skin test antigen, a preparation of inactivated mumps virus, has been used with other antigens to assess the status of cell-mediated immunity. A positive reaction may indicate previous infection with mumps virus

but it is not considered to be very reliable. It should not be given to patients hypersensitive to egg protein.

Muramidase Hydrochloride

N-Acetylmuramide Glycanohydrolase Hydrochloride; E1105 (muramidase); Globulin G; Hydrochloride; Hidrocloruro de lisozima; Lysozyme Hydrochloride; Muramidasa, hidrocloruro de; Лизоцима Гидрохлорид.

CAS — 9001-63-2 (muramidase); 9066-59-5 (muramidase hydrochloride).

ATC — D06BB07; J05AX02.

ATC Vet — QD06BB07; QJ05AX02.

UNII — 4YRW73H69V.

Pharmacopoeias. In *Jpn.*

Profile

Muramidase is a mucopolysaccharidase normally present in saliva and other tissues and secretions. It is active against Gram-positive bacteria, possibly by transforming the insoluble polysaccharides of the cell wall to soluble mucopeptides. It is also thought to be active against some viruses and some Gram-negative bacteria.

Muramidase has been given, usually as the hydrochloride, to patients with herpes zoster and other painful viral infections, and for mouth and respiratory-tract disorders. It has been used with antibacterials in an attempt to enhance their activity. Sensitivity reactions have been reported.

Adverse effects. A report[1] of a toxic epidermal necrolysis-type drug eruption in a patient who took an oral cold preparation containing muramidase chloride, which was considered to be the probable cause. The patient's condition improved after intravenous corticosteroid therapy.

1. Kobayashi M, *et al.* A case of toxic epidermal necrolysis-type drug eruption induced by oral lysozyme chloride. *J Dermatol* 2000; 27: 401–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Murazyme; *Hong Kong*: CP-Lyso; Eurozyme; Flemizyme; Jemizym; Leftose†; Lysosmin†; Neuzym; Qualizyme; Uni-Zyme†; Visozyme†; *Jpn*: Leftose; Neuzym; *Malaysia*: B-Zyme; Neuzym; Noflux; *Singapore*: Leftose; Lyzyme; Neuflo; Neuzym; *Thai.*: Leftose†.

Multi-ingredient Preparations. *Braz.*: Colpistar; Tricomax; *Fr.*: Cantalene; Glossithiase; Hexalyse; Lyso-6; Lysopaine; *Ger.*: Frubienzym†; *Gr.*: Lyso-6; Lysopaine; Lysoril; Sopain-Plus; *Hong Kong*: Eye-Ruby L†; Hexalyse; Quadezyme; *Ital.*: Narlisim; *Port.*: Narizima; *Rus.*: Bifilis (Бифилис); Hexalyse (Гексализ); Lysobact (Лизобакт); *Singapore*: Biotene; Biotene; Luvena Prebiotic; OralSeven; OralSeven; OralSeven; *Spain*: Lizipaina; Rino Dexa; Trofalgon; *Switz.*: Arbid-top; Lysopaine N; Lysopaine†; Mebucasol †; Sangerol; *Thai.*: Siduol; *UK*: Biotene Dry Mouth; *Ukr.*: Hexalyse (Гексализ); Lisak (Лизак); Lizak (Лизак); Lysobact (Лизобакт); *USA*: Bio-Zyme; Biotene with Calcium.

Poisonous Mushrooms or Toadstools

Champignons vénéneux; Giftpilze; Setas venenosas.

CAS — 23109-05-9 (α-amanitin); 21150-22-1 (β-amanitin); 21150-23-2 (γ-amanitin); 58919-61-2 (coprine); 16568-02-8 (gyromitrin); 2552-55-8 (ibotenic acid); 60-34-4 (methylhydrazine); 300-54-9 (muscarine); 2763-96-4 (muscimol); 37338-80-0 (orellanine); 17466-45-4 (phalloidin); 28227-92-1 (phalloin); 39412-56-1 (phallolysin).

Classification

This monograph describes poisonous mushrooms often known as toadstools, their toxins, toxic effects, and the treatment of those effects. Their only use is in homoeopathic medicine (see below). *Amanita muscaria* and *Psilocybe* spp. are abused for their psychoactive properties (see also Psilocin, p. 2599.1).

Mushrooms can be classified into 8 groups according to their principal toxins and toxic effects:

- *Group I.* Most deaths due to mushroom poisoning follow the ingestion of mushrooms containing cyclopeptides and among these mushrooms *Amanita phalloides* ('death cap') has been reported to be responsible for 90% of all mushroom fatalities. The cyclopeptides are a group of heat-stable cyclic polypeptides with molecular weights ranging from 800 to 1100 and include the amatoxins (α-, β-, γ-amanitin) and phallotoxins (phalloidin, phaloin, phallolysin). Other mushrooms containing cyclopeptides include *A. verna* ('deadly agaric', 'fool's mushroom'), *A. virosa*, ('destroying angel') and *A. bisporigera* ('white destroying angel'), and *Galerina autumnalis*, *G. marginata*, and *G. venenata*.
- *Group II.* Although *A. muscaria* ('fly agaric') and *A. pantherina* ('panther cap', 'false blusher') may contain small amounts of muscarine, the antimuscarinic effects of the hallucinogenic agent muscimol and the insecticidal agent ibotenic acid usually predominate.
- *Group III.* Many species of *Gyromitra* contain toxins known as gyromitrins that decompose to release methylhydrazine (monomethylhydrazine; MMH) an inhibitor of the coenzyme pyridoxal phosphate.
- *Group IV.* Mushrooms whose principal toxin is muscarine include many of the *Clitocybe* and *Inocybe* spp. *A. muscaria* and *A. pantherina* (see above) may also contain small amounts.
- *Group V. Coprinus atramentarius* ('ink cap') contains the compound coprine, one of whose metabolites is an inhibitor of acetaldehyde dehydrogenase and it may therefore produce 'disulfiram-like' symptoms after drinking alcohol.
- *Group VI.* Mushrooms that may contain the hallucinogenic indoles psilocin and psilocybine include species of *Psilocybe*, *Panaeolus*, *Gymnopilus*, *Stropharia*, and *Conocybe*.
- *Group VII.* Many mushrooms that only act as gastrointestinal irritants and do not produce systemic effects are included in this group.
- *Group VIII.* A further group has sometimes been used to classify some species of *Cortinarius* that contain a renal toxin thought by some to be orellanine, but whose exact nature remains to be determined.

Uses

Several types of poisonous mushrooms have been used in homoeopathic medicines under the following names:

- *Amanita phalloides*: Agaricus phalloides; Agaricus phal; Agaricus bulbosus
- *Amanita muscaria*: Agaricus muscarius; Agaricus musc; Agar. m.
- *Coprinus stercorarius* (*Stropharia stercoraria*): Agaricus stercorarius; Agaricus ster; Aga. ster.
- *Russula emetica*: Agaricus emeticus; Agaricus emet; Agar. e.

Adverse Effects

The clinical course of poisoning due to mushrooms is related to their principal toxins:

- *Group I.* Initial symptoms may occur 6 to 24 hours after ingestion of mushrooms containing cyclopeptides, and usually consist of gastrointestinal effects such as abdominal pain, nausea, severe vomiting, and profuse diarrhoea similar to that in cholera. The patient may then appear to recover and be symptom-free for 2 to 3 days, although liver-enzyme values may be increasing. After this phase, the more serious toxic effects of the amatoxins become apparent and there are signs of hepatic, renal, cardiac, and CNS toxicity. Symptoms include jaundice, oliguria, anuria, hypoglycaemia, coagulopathies, circulatory collapse, convulsions, and coma. The mortality rate is high in this third phase, with death usually being due to hepatic failure following hepatic necrosis. Up to 90% of untreated patients may die, though the rate can be as low as 15 to 30% after treatment.
- *Group II.* The adverse effects of mushrooms containing ibotenic acid and muscimol usually occur within 2 hours of ingestion. Symptoms may include ataxia, euphoria, delirium, and hallucinations associated with other antimuscarinic effects. Fatalities are rare.
- *Group III.* Patients who have ingested mushrooms containing gyromitrins usually develop symptoms of poisoning within 6 to 24 hours. These consist initially of nausea, vomiting, abdominal pain, and muscle cramps, headache, dizziness and fatigue. Delirium, convulsions, coma, methaemoglobinaemia and haemolysis may also occur. Occasionally jaundice and hepatic necrosis lead to hepatic failure and death. Up to 40% of patients die.
- *Group IV.* Symptoms typical of 'cholinergic crisis' (see Adverse Effects of Neostigmine, p. 688.2) may appear about 30 minutes to 2 hours after ingestion of mushrooms containing muscarine. These include bradycardia, bronchospasm, salivation, perspiration, lachrymation, rhinorrhoea, involuntary urination and defaecation, and diarrhoea. Miosis, hypotension, and cardiac arrhythmias may also occur. Rarely death may follow due to cardiac arrest or respiratory-tract obstruction.
- *Group V.* Since one of the metabolites of coprine is an acetaldehyde dehydrogenase inhibitor, drinking alcohol, even up to several days after ingestion of mushrooms containing this compound, will produce symptoms similar to those of the 'disulfiram-alcohol' interaction (see Disulfiram, Adverse Effects, p. 2496.1). Fatalities are rare.
- *Group VI.* The adverse effects of ingestion of mushrooms containing psilocin and psilocybine are similar to those described under lysergide (p. 2547.2). Symptoms usually occur within about 30 minutes to 2 hours. Fatalities are rare.
- *Group VII.* Generally no treatment is required for adverse gastrointestinal effects seen with this group of mushrooms.
- *Group VIII.* There may be a delay of as long as 14 to 20 days before symptoms of poisoning due to *Cortinarius* appear. Patients will develop an intense thirst. Other symptoms usually include nausea, vomiting, diarrhoea, and anorexia. Muscle aching and spasms and a feeling of coldness may also occur. In severe cases renal failure may lead to death. It has been reported that up to 15% of patients die.

Pregnancy. α-Amanitine does not appear to cross the placental barrier, even during the acute phase of intoxication.[1]

1. Belliardo F, *et al.* Amatoxins do not cross the placental barrier. *Lancet* 1983; i: 1381.

Treatment of Adverse Effects

As there are no specific antidotes for the majority of cases of mushroom poisoning and the species involved is often unknown, treatment consists mainly of symptomatic and supportive measures. The stomach may be emptied by gastric lavage if the patient has not already vomited spontaneously. However, if presentation is delayed (because of the slow onset of symptoms seen with some types of mushrooms) measures to empty the stomach are unlikely to be beneficial. Activated charcoal may be of use in binding toxins in the gastrointestinal tract and preventing absorption. Determining the interval between ingestion and the onset of symptoms often helps to identify the type of mushrooms ingested. If possible specimens of the mushrooms or a sample of the stomach contents should be sent to an expert mycologist for identification. Particular attention should be paid to intravenous replacement of fluids and electrolytes especially if vomiting and diarrhoea are severe. If the ingestion of hepatotoxic or nephrotoxic mushrooms is suspected liver and renal function should be monitored.

Since some mushrooms contain a wide range of toxins and patients may have ingested more than one species, specific therapy should only be instituted after positive identification.

- *Group I.* There is little clinical evidence to support the efficacy of specific agents or treatments for the management of cyclopeptide poisoning. Drugs such as benzylpenicillin, silymarin or silibinin have been given to try to protect the liver against the hepatotoxic effects of the amatoxins. Exchange transfusions, haemodialysis, or charcoal haemoperfusion have been tried to facilitate amatoxin removal. The removal of bile via a duodenal tube left *in situ* has been suggested to reduce enterohepatic circulation of amatoxins. Forced diuresis has also been advocated. Liver transplantation may be required for progressive hepatic failure. A radioimmunoassay for the detection of amatoxins is available in some countries to confirm a diagnosis of cyclopeptide poisoning.
- *Group II.* Specific treatment is usually only required if symptoms are severe. Physostigmine has been used to treat antimuscarinic symptoms. As mushrooms containing ibotenic acid and muscimol may also contain small amounts of muscarine, atropine may be required to control muscarinic symptoms.
- *Group III.* Pyridoxine hydrochloride has been given as an intravenous infusion as specific therapy to overcome the inhibition of pyridoxal phosphate by methylhydrazine, but the use of large doses of pyridoxine might itself produce adverse neurological effects. Methylthioninium chloride may be required if methaemoglobinaemia is severe.
- *Group IV.* Atropine sulfate may be required to control the symptoms of muscarine poisoning but it should only be used if definite muscarinic symptoms are present.
- *Group V.* There is no specific treatment for the 'disulfiram-alcohol' reaction except for the maintenance of blood pressure.
- *Group VI.* If symptoms are severe some patients may require sedation with diazepam.

General reviews.

1. Köppel C. Clinical symptomatology and management of mushroom poisoning. *Toxicon* 1993; 31: 1513–40.

Amanita phalloides. The use of specific antidotes in the treatment of poisoning due to *Amanita phalloides* remains controversial. Acetylcysteine, benzylpenicillin, sulfamethoxazole, thioctic acid, cytochrome C, ascorbic acid, insulin, growth hormone, silymarin or silibinin, and corticosteroids have all been used or suggested. Evidence to support most of these is lacking;[1,2] there is limited evidence to support the use of silibinin and acetylcysteine, but benzylpenicillin, although widely used, does not have

proven efficacy.[1] In patients who develop fulminant liver failure the definitive treatment is liver transplantation.[1,2]

1. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; 40: 715–57.
2. Berger KJ, Guss DA. Mycotoxins revisited: part I. *J Emerg Med* 2005; 28: 53–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Hung.*: Spascupreel.

Black Mustard

Graine de Moutarde Noire; Mostarda Preta; Mostaza negra; Moutarde Jonciforme; Schwarzer Senfsame; Semen Sinapis; Semilla de Mostaza; Sinapis Nigra; Горчица Чёрная.

ATC Herb — HM02AW5003 (Brassica nigra: seed).

UNII — 8LTY55LQ8D.

Description. Black mustard is the dried ripe seeds of *Brassica nigra* (*B. sinapioides*) (Cruciferae).

Pharmacopoeias. In *Swiss* which allows *B. nigra*, *B. juncea*, and other species.

White Mustard

Mostaza blanca; Sinapis Alba; Горчица Белая.

UNII — 66SFD3EC0P (Sinapis alba); 25VR943RPP (Sinapis alba seed).

Description. White mustard is the dried ripe seeds of *Brassica alba* (Cruciferae).

Pharmacopoeias. *Chin.* allows *B. alba* or *B. juncea*.

Uses and Administration

Black and white mustard seeds have been used as emetics, in counter-irritant and rubefacient preparations, and as condiments. Black mustard seeds are the source of volatile mustard oil (p. 2646.1), which is composed largely of allyl isothiocyanate (p. 2436.3).

Adverse Effects

Hypersensitivity. A report of 2 cases of IgE-mediated anaphylaxis to mustard condiment.[1]

1. Vidal C, *et al.* Anaphylaxis to mustard. *Postgrad Med J* 1991; 67: 404.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mon.*: Autoplasme Vaillant; Sinapisme Rigollot.

Multi-ingredient Preparations. *Pol.*: Reumobonisol.

Homoeopathic Preparations. *Austral.*: Hay Fever; *Austria*: Delufen; *Ger.*: Sinapis nigra N Oligoplex; *Rus.*: Aphlubin-Naze (Афлубин-Назе); Delufen (Делуфен); *Ukr.*: Delufen (Делуфен).

Myrrh

Gum Myrrh; Gummiresina Myrrha; Mira; Mirhami; Mirra; Mirrha; Myrhovníková klejopryskyřice; Myrra; Myrrha; Myrrhe; Миррa.

CAS — 9000-45-7 (Myrrh); 8016-37-3 (myrrh oil).

ATC Herb — HA03AW5016 (Commiphora myrrha: resin); HA01WC5002 (Commiphora myrrha: resin).

UNII — JC7TGJ1F3L.

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

Ph. Eur. 8: (Myrrh). A gum-resin, hardened in air, obtained from the stem and branches of *Commiphora molmol* and/or other species of *Commiphora*. Protect from light.

USP 36: (Myrrh). The oleo-gum resin obtained from the stems and branches of *Commiphora molmol* and other related species of *Commiphora* (Burseraceae) other than *C. mukul*. Store in airtight containers in a dry place.

Profile

The principal source of myrrh is *Commiphora myrrha* (*C. molmol*) (Burseraceae). Myrrh is astringent to mucous membranes; the tincture is used in mouthwashes and gargles for inflammatory disorders of the mouth and pharynx. It has also been used as a carminative. Myrrh has been tried in the treatment of schistosomiasis and fascioliasis.

Myrrh should not be confused with guggul (p. 2523.2) to which it is related.

Myrrh oil is used in aromatherapy.

Contact dermatitis has been reported.

Helminth infections. Myrrh was of benefit in a small study[1] of 7 patients with fascioliasis and in another study[2] of 204 patients with schistosomiasis. However, it showed low cure rates in the treatment of schistosomiasis when compared with praziquantel.[3,4]

1. Massoud A, *et al.* Preliminary study of therapeutic efficacy of a new fasciolicidal drug derived from Commiphora molmol (myrrh). *Am J Trop Med Hyg* 2001; 65: 96–9.
2. Sheir Z, *et al.* A safe, effective, herbal antischistosomal therapy derived from myrrh. *Am J Trop Med Hyg* 2001; 65: 700–4.
3. Botros S, *et al.* Efficacy of mirazid in comparison with praziquantel in Egyptian Schistosoma mansoni-infected school children and households. *Am J Trop Med Hyg* 2005; 72: 119–23.
4. Barakat R, *et al.* Efficacy of myrrh in the treatment of human schistosomiasis mansoni. *Am J Trop Med Hyg* 2005; 73: 365–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Inspirol P†; *Rus.*: Myrtoplex (Миртоплекс).

Multi-ingredient Preparations. *Arg.*: Parodontax Fluor; *Austral.*: Eczema Relief†; Herbal Throat Spray; *Austria*: Brady's-Magentropfen; Dentinox†; Parodontax†; Pervivo; *Braz.*: Paratonico†; Parodontax†; Vitonico; *Chile*: Astrijesan; *Cz.*: Dr Theiss Schweden Kraeuter†; Dr Theiss Schwedenbitter†; Original Schwedenbitter; *Denm.*: Dolodent; *Fr.*: Tigre de Chine; *Ger.*: Infi-tract V; Mint-Lysoform; Myrrhinil-Intest; Ratanhia comp†; Repha-Os†; *Hong Kong*: Ad-Muc; *Hung.*: Bano Svedkeseru; Bittner; *Philipp.*: BSI Medicated Plaster; *Pol.*: Pervivo; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Helmontskruie†; Lewensessens; *Spain*: Buco Regis; *Switz.*: Baume Zeller; Kernosan Eau Dentifrice†; Pommade au Baume; Sanogencive; *UK*: Herbal Indigestion Naturtabs; HRI Golden Seal Digestive; Indigestion and Flatulence; Vocalzone; Wind & Dyspepsia Relief; *Ukr.*: Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. *UK*: Medicinal Gargle.

Pharmacopoeial Preparations

Ph. Eur.: Myrrh Tincture;

USP 36: Myrrh Topical Solution.

Myrtillus

Baccae Myrtilli; Bilberry; Blăbăr (bilberry fruit); Blaeberry; Borůvkový plod; Fekete áfonya termés (bilberry fruit); Heidelbeere; Huckleberry; Hurtleberry; Mirtilo; Mėlynių uogos, džiovintos (bilberry fruit); Mustikka (bilberry fruit); Myrtille, fruit de (bilberry fruit); Myrtilli Fructus; Myrtilli fructus (bilberry fruit); Whortleberry; Черника Обыкновенная.

ATC Herb — HD08AW5005 (Vaccinium myrtillus: leaf); HA07XA5015 (Vaccinium myrtillus: fruit); HA10BX5005 (Vaccinium myrtillus: leaf).

UNII — 9P2U39H18W (Vaccinium myrtillus fruit); Y4U591OU70 (Vaccinium myrtillus leaf).

Pharmacopoeias. In *Eur.* (see p. vii). *US* includes Powdered Bilberry Extract.

Ph. Eur. 8: (Bilberry Fruit, Dried; Dried Bilberry BP 2014; Bilberry Fruit, Fresh; Fresh Bilberry BP 2014). The ripe fruit of *Vaccinium myrtillus*. It has a sweet and slightly astringent taste. The dried fruit contains a minimum of 1.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. The fresh or frozen fruit contains a minimum of 0.30% of anthocyanins, expressed as cyanidin-3-glucoside chloride (chrysanthemin, $C_{21}H_{21}ClO_{11}$ = 484.8), calculated with reference to the dried drug. The frozen fruit should be stored at or below -18 degrees.

Profile

Myrtillus has diuretic and astringent properties. It has been used for ophthalmic and circulatory disorders and for diarrhoea.

Homoeopathy

Myrtillus has been used in homoeopathic medicines under the following names: Vaccinium myrtillus; Vaccinium; Vac. myrt.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Miralis; *Ger.*: Difrarel†; *India*: Gloeye; *Indon.*: Lanavision; *Ital.*: Mirtilene Forte; Tegens; *Malaysia*: Natberry; *Pol.*: Bilberin†; Fibs; *Port.*: Difrarel; Tegens; *Rus.*: Mirtilene Forte (Миртилене Форте); *Switz.*: Myrtaven.

Multi-ingredient Preparations. *Arg.*: Chiafibra; *Austral.*: Bilberry Plus Eye Health†; Bilberry Plus†; Extralife Eye-Care†; Extralife Leg-Care†; PM Eye Tonic; Pygno-Vite†; St Mary's Thistle Plus†; Vision-Eze†; *Austria*: Amersan; *Canad.*: Visionex; *China*: Difrarel (通法明); *Cz.*: Amersan; Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Tormentan; Urcyston Planta; *Fr.*: Antioxydant F4; Bion 3 Seniors; Blue Berry; Clediat; Difrarel E; Difrarel; Difravision; Glycepure; Phyltalzeal; Stomargil; Sun Vue; Tone; *Hong Kong*: Mega-Antioxidant†; PM Eye Tonic†; *Hung.*: Diabess; Difrarel E†; *India*: GV-24; I-Lute; *Indon.*: Berry Vision; Bioretin†; Eyebright; Eyevit; Kapset; Lanavision Plus; Lanavision; Lubire; Lutevision Extra; Lutevision†; Matase; Matovit AX; Matovit Fifty; Matovit; Natureyes; nutrivision; Nuvision; Ocu-V; Ocugard; Oculex; Oculex; Opibright; Optha-LL; Optimax Plus; Optimax; Proliva; Proview; Retop; Visivit; Vita-Vision; Vitop; *Israel*: Opti-Safe†; *Ital.*: Alvear con Ginseng; Angiorex Complex; Angioton; Api Baby; Bebimix†; Biolactine; Capill; Dermilla Flebozin†; Eu-Visus; Euretin; Evamilk; Flavogin Plus; Flebo-Si†; Flebofort; Flebofort; Ginecistin; Lactovit; Levital Plus; Lik-Gel†; Lipaven; Macvit; Memovigor; Mentvis; Mirtex P; Mirtilene; Mirtilux; Mirtilux; Mirtiros; Neomyrt Plus; Nerex; Pik Gel; Promix 3; Retinovit; Rivuclin; The Ginseng King†; Troca Vit; Tussol; Ultravisin; Visu-ton; Vitalmix Complex; Vitreolux; *Malaysia*: Natberry Extra; Natberry Plus; *Philipp.*: iiCare; *Pol.*: Biovision; Pelogel; Reumosol; *Rus.*: Brusniver (Брусниver); Multimax for Eyes (Мультимакс Для Глаз); Strix (Стрикс); *Singapore*: EyeMax; Nutrivision†; Visionex†; *Spain*: Mirtilus†; *Switz.*: Herba-Vision Myrtillus; *UK*: Se-Power; Vision-Max; *Ukr.*: Lipomin (Липомин); Liponorm (Липонорм); Memory Booster (Мемори Бустер); Oko-Health (Око-хелс); Osteoartisi Max (Остеоартиси Макс); Vitrum Foreyes Forte (Витрум Форайз Форте); Vizivit (Визивит); *USA*: Clinical Nutrients 50-Plus Men; Diabetiks.

Homoeopathic Preparations. *Fr.*: Diabene; Diacure; Poconeol no 35; *Rus.*: Mirticam (Миртикам).

Pharmacopoeial Preparations

Ph. Eur.: Fresh Bilberry Fruit Dry Extract, Refined and Standardised.

Myrtle

Arrayán; Mirto; Myrte; Мирт Обыкновенный.

CAS — 8008-46-6 (myrtle oil); 8002-55-9 (myrtol).

UNII — 367E55FXGW.

NOTE. Distinguish from Myrtillus, above, derived from *Vaccinium myrtillus*.

Profile

Myrtle (*Myrtus communis*, Myrtaceae) has been included in herbal preparations for cough.

Myrtle oil is obtained from the leaves and twigs. Myrtle oil is included in preparations for disorders of the upper respiratory tract and is used in aromatherapy.

The term myrtol has been used to describe an extract of myrtle, standardised on its content of α-pinene, *d*-limonene, and cineole. It is used for respiratory-tract disorders.

References.

1. Matthys H, *et al.* Efficacy and tolerability of myrtol standardized in acute bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. *Arzneimittelforschung* 2000; 50: 700–11.
2. Gündüz GT, *et al.* Efficacy of myrtle oil against Salmonella typhimurium on fresh produce. *Int J Food Microbiol* 2009; 130: 147–50.
3. Babaee N, *et al.* The efficacy of a paste containing Myrtus communis (myrtle) in the management of recurrent aphthous stomatitis: a randomized controlled trial. *Clin Oral Investig* 2010; 14: 65–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Gelomyrtol; *Fr.*: Myrtine; *Ger.*: Gelomyrtol; *Gr.*: Gelomyrtol; *Hong Kong*: Gelomyrtol; *Neth.*: Gelodurat; *Rus.*: Gelomyrtol (Геломиртол); *Switz.*: Gelomyrtol; *Thai.*: Gelomyrtol†; *Ukr.*: Gelomyrtol (Геломиртол).

Multi-ingredient Preparations. *Austria*: Tetra-Gelomyrtol†; *Fr.*: Nazinette du Docteur Gilbert; Percutalgin'Phyto; *Ger.*: Tetra-Gelomyrtol; *Rus.*: Entoban (Энтобан); *Switz.*: Gelodurat; *Ukr.*: Entoban (Энтобан).

Nabiximols *(USAN)*

GW-1000.

CAS — 56575-23-6.

ATC — N02BG10.

ATC Vet — QN02BG10.

UNII — K4H93P747Q.

Description. Nabiximols is defined as a mixture of two cannabis extracts:

Component A, which is a highly characterized botanical extract of a defined chemotype of *Cannabis sativa* L. The major chemical constituent is the cannabinoid dronabinol (Δ^9-tetrahydrocannabinol; THC). Minor constituents include related cannabinoids and non-cannabinoid components α - and *trans*-caryophyllenes.

Component B, which is a highly characterized botanical extract of a defined chemotype of *Cannabis sativa* L. The major chemical constituent is the cannabinoid cannabidiol (CBD). Minor constituents include related cannabinoids and non-cannabinoid components α - and *trans*-caryophyllenes.

The names Tetranabinex and Nabidiolex have been used as trade marks for components A and B, respectively.

Profile

Nabiximols is a combination of two cannabis (p. 2467.1) extracts obtained from chemically and genetically characterised plants of *Cannabis sativa*. The principal active components of the extracts are the cannabinoids, dronabinol (Δ^9-tetrahydrocannabinol, see p. 1840.1) and cannabidiol (p. 2467.1). Nabiximols is used in a buccal spray preparation as adjunctive treatment for the symptomatic relief of moderate to severe spasticity due to multiple sclerosis in adults who have not responded adequately to other therapy and who show clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. It may also be of benefit as adjunctive analgesic treatment for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis. This same preparation is also used as adjunctive analgesic treatment in adult patients with advanced cancer who have moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Nabiximols is given in a dose equivalent to 2.7 mg dronabinol and 2.5 mg cannabidiol in each 100 microlitre spray. The dose is titrated over 14 days to find the optimum dose, which is normally between 4 and 8 sprays daily, up to a usual maximum of 12 sprays daily. The dose on the first day is 1 spray once or twice daily, with gradual incremental increases thereafter of no more than 1 additional spray per day. The gap between sprays should be at least 15 minutes. The timing of sprays varies between patients but in general the morning dose should be taken before midday, and the afternoon/evening dose between 4 pm and bedtime. Once the optimum daily dose has been reached, patients may spread the dose throughout the day depending on individual response and tolerability. The spray should be directed at different sites on the oromucosal surface changing the site with each use. The spray should not be directed towards the pharynx, nor should it be inhaled, and it should not be used intranasally.

Use is contra-indicated in patients with a history of psychosis or other serious psychiatric disorders (other than reactive depression). Nabiximols is also not recommended in patients with serious cardiovascular disease. Mild or moderate dizziness is common during the first few weeks of treatment.

For references to studies of nabiximols and other potential uses of cannabinoids, see under Cannabis, p. 2468.1.

Breast feeding. Nabiximols is contra-indicated in breast feeding because of the considerable levels of cannabinoids likely in maternal breast milk and the potential for developmental adverse effects in the nursing infant.

Pregnancy. Licensed product information for nabiximols generally contra-indicates use in pregnancy, and advises that female patients of child-bearing potential, or male patients with partners in this category, should use reliable contraceptive precautions during treatment and for 3 months afterwards.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Sativex; *Cz.*: Sativex; *Denm.*: Sativex; *Fin.*: Sativex; *Ger.*: Sativex; *Israel*: Sativex; *Neth.*: Sativex; *Norw.*: Sativex; *NZ*: Sativex; *Spain*: Sativex; *Swed.*: Sativex; *UK*: Sativex.

Nadide *(BAN, USAN, rINN)*

Co-I; Codehydrogenase I; Coenzima I; Coenzyme I; Difosfopiridina nucleótido; Diphosphopyridine Nucleotide; DPN; NAD; Nadida; Nadidum; Nicotinamida adenina dinucleot; Nicotinamide Adenine Dinucleotide; NSC-20272; Надид.

1-(3-Carbamoylpyridinio)-β-D-ribofuranoside 5-(adenosine-5′-pyrophosphate).

$C_{21}H_{27}N_7O_{14}P_2$=663.4

CAS — 53-84-9.

UNII — 0U46U6E8UK.

Profile

Nadide is a naturally occurring coenzyme claimed to be of value in the treatment of alcohol and opioid addiction. The reduced form of nadide, NADH, has been used in the management of chronic fatigue syndrome.

Parkinsonism. The reduced form of nadide, NADH (β-NADH; reduced DPN) and its phosphate derivative (NADPH) have been given in the management of Parkinson's disease in an attempt to enhance endogenous dopamine synthesis by stimulating the enzyme tyrosine hydroxylase. Although some beneficial effects have been reported in several case series, a placebo-controlled study failed to find any evidence of efficacy and the routine use of NADH has not been recommended.[1]

1. Swerdlow RH. Is NADH effective in the treatment of Parkinson's disease? *Drugs Aging* 1998; 13: 263–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: DPN†; *Spain*: Nad†.

Multi-ingredient Preparations. *Philipp.*: Enervon-C.

Homoeopathic Preparations. *Canad.*: Cutisitum†; Hepar Compositum; Ubicoenzyme; *Cz.*: Zeel Salbe†; *Hung.*: Zeel; *Rus.*: Zeel T (Цем. Т).

Nafamostat Mesilate *(rINNM)*

FUT-175; Mesilato de nafamostat; Nafamostat Mésilate de; Nafamostat, mesilato de; Nafamostat Mesylate (USAN); Nafamostati Mesilas; Нафамостата Мезилат.

6-Amidino-2-naphthyl *p*-guanidinobenzoate dimethanesulfonate.

$C_{21}H_{25}N_5O_8S_2$=539.6

CAS — 81525-10-2 (nafamostat); 82956-11-4 (nafamostat mesilate).

UNII — 1D2774921W.

Pharmacopoeias. In *Jpn.*

Profile

Nafamostat is a proteolytic enzyme inhibitor that has been used as the mesilate in the treatment of acute pancreatitis and disseminated intravascular coagulation, and as an anticoagulant in haemodialysis.

Hyperkalaemia has been reported.

References.

1. Yanamoto H, *et al.* Therapeutic trial of cerebral vasospasm with the serine protease inhibitor, FUT-175, administered in the acute stage after subarachnoid hemorrhage. *Neurosurgery* 1992; 30: 358–63.
2. Akizawa T, *et al.* Nafamostat mesilate: a regional anticoagulant for haemodialysis in patients at high risk for bleeding. *Nephron* 1993; 64: 376–81.
3. Miyata T, *et al.* Effectiveness of nafamostat mesilate on glomerulonephritis in immune-complex diseases. *Lancet* 1993; 341: 1353.
4. Murase M, *et al.* Nafamostat mesilate reduces blood loss during open heart surgery. *Circulation* 1993; 88: 432–6.
5. Kitagawa H, *et al.* Hyperkalaemia due to nafamostat mesylate. *N Engl J Med* 1995; 332: 687.
6. Yamazato M, *et al.* Severe abdominal pain associated with allergic reaction to nafamostat mesilate in a chronic hemodialysis patient. *Intern Med* 2002; 41: 864–6.
7. Kaminishi Y, *et al.* Effects of nafamostat mesilate and minimal-dose aprotinin on blood-foreign surface interactions in cardiopulmonary bypass. *Ann Thorac Surg* 2004; 77: 644–50.
8. Ota T, *et al.* Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage. *Interact Cardiovasc Thorac Surg* 2007; 6: 270–3.

Naphthylacetic Acid

Naftilacético, ácido; 1-Naphthaleneacetic Acid; 1-Naphthylacetic Acid; Нафтилуксусная Кислота.

$C_{12}H_{10}O_2$=186.2

CAS — 86-87-3.

UNII — 33T7G7757C.

Profile

Naphthylacetic acid has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Galle-Donau; *China*: Galle-Donau (加味).

Natalizumab *(BAN, rINN)*

Natalizumabum; Натализумаб.

Immunoglobulin G 4 (human-mouse monoclonal AN100226 4-chain antihuman integrin-4), disulfide with human-mouse monoclonal AN100226 light chain, dimer.

CAS — 189261-10-7.

ATC — L04AA23.

ATC Vet — QL04AA23.

UNII — 3JB47N2Q2P.

NOTE. The name Antegren has been used as a trade mark for natalizumab.

Uses and Administration

Natalizumab is a recombinant humanised monoclonal antibody raised against human α4 integrin that is used as monotherapy to prevent relapses and delay progression of disability in patients with highly active relapsing-remitting multiple sclerosis. It is also used for inducing and maintaining response and remission in moderate to severe Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). However, because of an increased risk of progressive multifocal leukoencephalopathy (PML) its availability is restricted, and use is limited to patients who have had an inadequate response to, or are unable to tolerate, other therapies. A baseline magnetic resonance imaging scan must be done before natalizumab is started in order to differentiate newly developed lesions from pre-existing lesions. Patients should be evaluated for signs and symptoms of PML at 3 and 6 months after the first dose, then every 6 months thereafter. Natalizumab must be discontinued at the first sign of PML or other opportunistic infection developing; treatment may resume if this diagnosis is excluded, but should be permanently discontinued if confirmed.

Patients who were previously taking interferon beta or glatiramer acetate may switch directly to natalizumab provided there are no treatment-related adverse effects such as neutropenia; blood counts must return to normal before starting natalizumab. Patients who have been receiving immunosuppressants such as azathioprine and cyclophosphamide must not start natalizumab until it has been confirmed that they are no longer immunocompromised. Likewise, the pharmacodynamic effects of natalizumab remain for about 12 weeks after stopping treatment, and therefore a wash-out period may be appropriate on stopping natalizumab before giving immunosuppressive drugs.

Natalizumab 300 mg is given by intravenous infusion once every 4 weeks. The dose is diluted in 100 mL of sodium chloride 0.9% and given over about 1 hour. The patient should be observed during the infusion and for a further hour after it is complete; the infusion should be stopped if a hypersensitivity reaction occurs and treatment with natalizumab permanently discontinued. Treatment should also be discontinued if there is evidence of persistent raised antibodies to natalizumab since these reduce efficacy and increase the risk of hypersensitivity reactions. Continuation of therapy in multiple sclerosis patients who have shown no benefit after 6 months should be reconsidered. In the treatment of Crohn's disease, natalizumab should be stopped if patients have not obtained therapeutic benefit after 12 weeks of induction therapy or when patients are unable to discontinue chronic concomitant corticosteroid use within 6 months of starting natalizumab.

Natalizumab has also been investigated for the treatment of ulcerative colitis.

References.

1. Sweet BV. Natalizumab update. *Am J Health-Syst Pharm* 2007; 64: 705–16.

Inflammatory bowel disease. The efficacy and safety of natalizumab in the treatment of *Crohn's disease* have been reviewed, including proposed mechanisms for the role of α4 integrins in the immunopathogenesis of inflammatory bowel disease (p. 1808.3).[1,2] A systematic review[3] of controlled studies of the use of natalizumab in the treatment of Crohn's disease concluded that it is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease, particularly those with active inflammation or chronically active disease despite use of conventional treatment. However, this benefit must be weighed against the risks of developing progressive multifocal leukoencephalopathy.

Natalizumab is also under investigation for *ulcerative colitis*.[4]

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; 39: 1833–43.
2. Lanzarotto F, *et al.* Novel treatment options for inflammatory bowel disease: targeting α 4 integrin. *Drugs* 2006; 66: 1179–89.
3. MacDonald JK, McDonald JWD. Natalizumab for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
4. Feagan BG, *et al.* Treatment of ulcerative colitis with a humanized antibody to the α 4 β 7 integrin. *N Engl J Med* 2005; 352: 2499–2507.

Multiple sclerosis. The efficacy and safety of natalizumab in the treatment of multiple sclerosis (p. 996.3) have been reviewed,[1-4] including proposed mechanisms for the role of α4 integrins in its immunopathogenesis.[5,6] Randomised controlled studies[7-10] showed beneficial results in suppressing inflammatory lesions and reducing the frequency of relapse. Subsequent review[11] of the data from the AFFIRM[8] and SENTINEL studies[9] showed reduction of visual loss. In the SENTINEL study,[9] natalizumab was given with interferon beta, a combination that may have contributed to the development of progressive multifocal leukoencephalopathy in 2 of the study patients, one of whom died (see Infections, p. 2568.2). In the GLANCE study,[12] the rate of development of new active MRI lesions was lower when natalizumab was given as add-on therapy to patients who had suffered at least one relapse while taking glatiramer acetate than with glatiramer acetate alone. Although there was no evidence of PML during this study, further study of natalizumab given with glatiramer acetate was stopped because of the occurrence of PML

reported by other workers when natalizumab was given as add-on therapy to interferon beta. Natalizumab is currently licensed only as monotherapy. New and enlarging lesions seen in patients 15 months after stopping natalizumab treatment[13] has raised the possibility of a rebound effect resulting in disease progression. However, data from another study[14] that followed up patients for 14 months after stopping therapy do not support these findings. Due to differing numbers of natalizumab exposures per patient between these two studies, it has been suggested[15] that a rebound effect is more likely to occur in patients who have short-term treatment.

1. Keeley KA, *et al.* Natalizumab for the treatment of multiple sclerosis and Crohn's disease. *Ann Pharmacother* 2005; 39: 1833–43.
2. Ransohoff RM. Natalizumab for multiple sclerosis. *N Engl J Med* 2007; 356: 2622–9.
3. Goodin DS, *et al.* The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; 71: 766–73.
4. Anonymous. Natalizumab for multiple sclerosis? *Drug Ther Bull* 2008; 46: 69–72.
5. Rice GPA, *et al.* Anti-α 4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology* 2005; 64: 1336–42.
6. Kivisäkk P, *et al.* Natalizumab treatment is associated with peripheral sequestration of proinflammatory T cells. *Neurology* 2009; 72: 1922–30.
7. Miller DH, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; 348: 15–23.
8. Polman CH, *et al.* AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899–910.
9. Rudick RA, *et al.* SENTINEL investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 911–23.
10. Miller DH, *et al.* AFFIRM Investigators. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; 68: 1390–1401.
11. Balcer LJ, *et al.* AFFIRM and SENTINEL investigators. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007; 68: 1299–1304.
12. Goodman AD, *et al.* GLANCE Investigators. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology* 2009; 72: 806–12.
13. Vellinga MM, *et al.* Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. *Neurology* 2008; 70: 1150–1.
14. Stüve O, *et al.* Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. *Neurology* 2009; 72: 396–401.
15. Schiess N, Calabresi PA. Natalizumab: bound to rebound? *Neurology* 2009; 72: 392–3.

Adverse Effects and Precautions

Natalizumab commonly causes infusion-related reactions including headache, dizziness, fatigue, urticaria, pruritus, rash, fever, rigors, nausea, hypotension, flushing, dyspnoea, and chest pain. Serious hypersensitivity reactions such as anaphylaxis can also occur. These reactions are usually associated with antibodies to natalizumab. The presence of these antibodies results in reduced serum concentrations and efficacy of natalizumab. The risk of infection is increased and there have been a few cases of progressive multifocal leukoencephalopathy (PML) reported; all patients should be monitored and if signs or symptoms of PML appear treatment should be withheld pending investigation. The risk of developing PML increases with treatment duration. Immune reconstitution inflammatory syndrome has been reported in patients who discontinued natalizumab after developing PML, and in almost all cases, it occurred after plasma exchange was used to eliminate natalizumab from the circulation. Clinically significant hepatotoxicity has also been reported with natalizumab and treatment should be stopped if there is evidence of jaundice or other significant liver injury.

Natalizumab is contra-indicated in patients who have previously had PML. It is also contra-indicated in patients with, or at risk for, opportunistic infections, and in those with malignancies. Patients with significantly compromised immune systems should not generally be given natalizumab.

Antibody formation. The incidence and clinical effects of antibody formation to natalizumab therapy in patients with relapsing multiple sclerosis were studied in the AFFIRM and SENTINEL studies.[1] Of 625 patients treated with natalizumab in the AFFIRM study 20 (3%) were transiently positive for antibodies to natalizumab and 37 (6%) were persistently positive. Equivalent figures for 585 natalizumab-treated patients in the SENTINEL study were 32 (5%) and 38 (6%) respectively. Overall the presence of antibodies was generally correlated with reduced serum concentrations of natalizumab and a poorer treatment response, efficacy being restored in those patients who became antibody-negative during therapy. Antibody-positive patients also had a higher incidence of infusion-related adverse effects, including hypersensitivity reactions (17 of the 37 persistently positive patients in the AFFIRM study). It is recommended that patients with suboptimal response to natalizumab or persistent infusion-related adverse effects should be considered for antibody testing. UK licensed product information warns that therapy should not be restarted in patients who remain positive for antibodies 6 weeks after interrupting an initial short exposure to natalizumab.

1. Calabresi PA, *et al.* The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; 69: 1391–1403.

Hypersensitivity. A review[1] of the data for patients who had hypersensitivity reactions in the AFFIRM study,[2] which included 627 patients in the natalizumab treatment group, found that there was a low incidence (<1%) of serious reactions described as anaphylactoid or anaphylactic. All patients with hypersensitivity reactions responded promptly to discontinuation of the infusion and standard pharmacotherapy as necessary (adrenaline, oxygen, and antihistamines with or without corticosteroids); all recovered fully about 1 to 2 hours after the end of the infusion. UK licensed product information warns that patients should be counselled on the importance of uninterrupted dosing, particularly in the early months of treatment; the risk for hypersensitivity reactions is greatest with early infusions and in patients who, after an initial short exposure to natalizumab, are re-exposed after a treatment-free period of 3 or more months.

1. Phillips JT, *et al.* Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology* 2006; 67: 1717–18. Correction. *ibid.* 2007; 68: 473.
2. Polman CH, *et al.* AFFIRM investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899–910.

Infections. Three cases of progressive multifocal leukoencephalopathy (an opportunistic infection of the brain caused by JC virus, a human polyomavirus) have been described in patients given natalizumab.[1-3] One patient[1] died after receiving natalizumab with azathioprine for Crohn's disease. The other patients[2,3] were given natalizumab with interferon beta for multiple sclerosis; one of these[2] also died. After these reports, the use of natalizumab was restricted (see Uses and Administration, p. 2567.2). A subsequent retrospective evaluation[4] of more than 3000 patients who had received natalizumab found no further cases. However, 2 further cases have subsequently been reported[5] in patients taking natalizumab as monotherapy for 14 months and 17 months; one of the patients had previously taken immunosuppressants. Further cases of PML continue to be reported[6] but the rate in patients who have received at least one infusion of natalizumab is below 1 in 1000 patients. However, the risk for developing PML appears to increase with the number of infusions and based on current worldwide data, the rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1000 patients.

1. Van Assche G, *et al.* Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; 353: 362–8.
2. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; 353: 369–74.
3. Langer-Gould A, *et al.* Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; 353: 375–81.
4. Yousry TA, *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; 354: 924–33.
5. FDA. Information for healthcare professionals: natalizumab injection for intravenous use (marketed as Tysabri) (issued Aug. 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126592.htm (accessed 11/03/10)
6. FDA. Information on natalizumab (marketed as Tysabri) (issued Sep. 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm (accessed 11/03/10)

Melanoma. Long-standing naevi in two women developed into melanoma shortly after starting natalizumab treatment for multiple sclerosis.[1]

1. Mullen JT, *et al.* Melanoma complicating treatment with natalizumab for multiple sclerosis. *N Engl J Med* 2008; 358: 647–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies natalizumab 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 06/10/11)

Interactions

Use with antineoplastics, immunosuppressants, or immunomodulators may further increase the risk of opportunistic infections including progressive multifocal leukoencephalopathy associated with natalizumab. Concurrent treatment with interferon beta or glatiramer acetate is contra-indicated.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Tysabri; ***Austria***: Tysabri; ***Belg.***: Tysabri; ***Braz.***: Tysabri; ***Canad.***: Tysabri; ***Cz.***: Tysabri; ***Denm.***: Tysabri; ***Fr.***: Tysabri; ***Ger.***: Tysabri; ***Gr.***: Tysabri; ***Hung.***: Tysabri; ***Irl.***: Tysabri; ***Israel***: Tysabri; ***Ital.***: Tysabri; ***Neth.***: Tysabri; ***Norw.***: Tysabri; ***NZ***: Tysabri; ***Pol.***: Tysabri; ***Port.***: Tysabri; ***Spain***: Tysabri; ***Swed.***: Tysabri; ***Switz.***: Tysabri; ***UK***: Tysabri; ***Ukr.***: Tizabri (Тизабри); ***USA***: Tysabri.

Neroli Oil

Aceite esencial de las flores del naranjo amargo; Aceite esencial de Neroli; Aurantii amari floris aetheroleum; Aurantii Amari Floris Aetheroleum (bitter-orange flower oil); Aurantii Amari Floris Etheroleum; Azahar, aceite esencial de; Bitter-Orange Flower Oil; Essencia de Azahar; Essência de Flor de Laranjeira; Karčiavaisių citrinmedžių žiedų eterinis aliejus (bitter-orange flower oil); Keserű narancs virág olaj (bitter-orange flower oil); Neroli aetheroleum; Néroli, huile essentielle de; Nerolíöl/Bitterorangenblütenöl; Neroliolja; Neroliöljy; Olejek z kwiatu pomarańczy gorzkiej; Oleum Neroli; Orange Flower Oil; Orange-flower Oil; Silice květů hořkého pomeranče; Неролиевое Масло.

UNII — D48GE91OXH.

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

Ph. Eur. 8: (Neroli Oil). A clear, pale yellow or dark yellow liquid with a characteristic odour obtained by steam distillation from the fresh flowers of *Citrus aurantium* subsp. *aurantium* (*C. aurantium* subsp. *amara*) (see under Bitter Orange, p. 2575.3). Relative density 0.863 to 0.880. Store in well-filled airtight containers at a temperature below 25 degrees. Protect from light.

Profile

Neroli oil is used as a flavour and in perfumery. It is also used in aromatherapy. Photosensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Agua Melisa Carminativa; ***Cz.***: Stopangin; ***Ital.***: Controller; ***Rus.***: Stopangin (Стопангин); ***Switz.***: Kemeol†; Nasmer free; Oculosan; ***Turk.***: Nevrol Cemal; ***Ukr.***: Stopangin (Стопангин).

Nerve Agents

Gases nerviosos.

Sarin

GB; Sarin.

Isopropyl methylphosphonofluoridate.

$C_4H_{10}FO_2P$=140.1

CAS — 107-44-8.

UNII — B4XG72QGFM.

Soman

GD; Somán.

Pinacolyl methylphosphonofluoridate.

$C_7H_{16}FO_2P$=182.2

CAS — 96-64-0.

Tabun

GA; Tabún.

Ethyl *N*-dimethylphosphoramidocyanidate.

$C_5H_{11}N_2O_2P$=162.1

CAS — 77-81-6.

VX

Methylphosphonothioic acid S-[2-[bis(1-methylethyl)amino] ethyl] O-ethyl ester.

$C_{11}H_{26}NO_2PS$=267.4

CAS — 50782-69-9.

UNII — 9A4381183B.

Profile

The nerve agents, sarin, soman, tabun, and VX (also referred to as 'nerve gases') used in chemical warfare are extremely potent inhibitors of cholinesterase. The effects of poisoning due to these agents, and their treatment, are similar to those for organophosphorus insecticides (p. 2158.3) but as the nerve agents have a much greater intrinsic toxicity the symptoms of poisoning are more severe. Pyridostigmine has been given prophylactically to personnel at risk from exposure to nerve agents (see p. 689.3).

References.

1. Ministry of Defence. *Medical manual of defence against chemical agents.* London: HMSO, 1987. (JSP312)
2. World MJ. Toxic gas trauma. *Lancet* 1995; 346: 260–1.

3. Nozaki H, *et al.* A case of VX poisoning and the difference from sarin. *Lancet* 1995; 346: 698–9.
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6. Holstege CP, *et al.* Chemical warfare: nerve agent poisoning. *Crit Care Clin* 1997; 13: 923–42.
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8. United States Army. *Medical Management of Chemical Casualties Handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense:1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/Red-Handbook/001TitlePage.htm (accessed 24/07/08)
9. Weinbroum AA, *et al.* Anaesthesia and critical care considerations in nerve agent warfare trauma casualties. *Resuscitation* 2000; 47: 113–23.
10. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; 44: 1–3.
11. Janowsky DS. Central anticholinergics to treat nerve-agent poisoning. *Lancet* 2002; 359: 265–6.
12. Anonymous. Nerve agents. *J R Army Med Corps* 2002; 148: 344–57.
13. Lee EC. Clinical manifestations of sarin nerve gas exposure. *JAMA* 2003; 290: 659–62.
14. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; 112: 648–58.
15. Newmark J. The birth of nerve agent warfare: lessons from Syed Abbas Poroutan. *Neurology* 2004; 62: 1590–6.

Neutral Red

CI Basic Red 5; Colour Index No. 50040; Neutral Red Chloride; Nuclear Fast Red; Rojo neutro; Rojo toluileno; Toluylene Red; Нейтральный Красный.

3-Amino-7-dimethylamino-2-methylphenazine hydrochloride.

$C_{15}H_{16}N_4.HCl$=288.8

CAS — 553-24-2.

UNII — 261QK3SSBH.

Profile

Neutral red is used as an indicator for alkalinity and for preparing neutral-red paper. It is also used as a stain in microscopy.

It is a photoactive dye that has been tried in photodynamic therapy of recurrent herpes simplex infections, but with limited success.

Niaouli Oil

Aceite esencial de niauli; Essence de Niaouli; Gomenol; Ниаули Масло.

UNII — D50K2T8FU (Melaleuca viridiflora oil); 22K2F1Y5HD (Melaleuca quinquenervia oil).

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

Ph. Eur. 8: (Niaouli Oil, Cineole Type; Niaouli Typo Cineolo Aetheroleum). An essential oil obtained by steam distillation from young leafy branches of *Melaleuca quinquenervia*. A colourless or pale yellow liquid with an aromatic odour of cineole. Store at a temperature below 25 degrees.

Profile

Niaouli oil is a volatile oil, obtained by distillation from the fresh leaves of *Melaleuca viridiflora* or *Melaleuca quinquenervia* (Myrtaceae). It contains cineole (p. 2479.1) and has similar actions to eucalyptus oil (p. 2501.2). It is an ingredient of many preparations. Typical indications include respiratory-tract congestion. Cajuput oil (p. 2464.1) and melaleuca oil (p. 2551.1) are also prepared from *Melaleuca* spp.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Gomenol; Gomenoleo; Huile Gomenolee; *Switz.*: Bronchomed.

Multi-ingredient Preparations. *Arg.*: Aseptobron; Aseptobron; Di-Neumobron; Medex Rub; No-Tos Adultos; Refenax Caramelos Expectorantes; *Braz.*: Algice; Gripsay; Ozonyl Aquoso; Ozonyl Expectorante; Ozonyl; Tetrapulmo†; *Fr.*: Arthro; Balsolene; Biogaze; Coquelusedal; Euphonyl Expectorant; Euvanol; Euvanol; Hexaquine; Olioseptil Nez-Gorge; Terpone Nourrisson†; Terpone; Thermo Gomenol; Vaseline Gomenolee; Veganix; Veino Gomenol; *Ital.*: Bron 6; Rinopaidolo; Rinovit; *Pol.*: Argol Grip; *Spain*: Brota Rectal Balsamico†; Pastillas Pectorales Kely†; Rinobanedif; Vapores Pyt†; Vitavox†; *Switz.*: DUL-X warm; Pulmex; Resorbane; *Turk.*: Buguseptil; Rinolar.

Nicergoline *(BAN, USAN, rINN)*

FI-6714; Nicergolin; Nicergolina; Nicergolinas; Nicergolinum; Nisergollini; Nisergolin; Ницерголин.

10α-Methoxy-1,6-dimethylergolin-8β-ylmethyl 5-bromonicotinate.

$C_{24}H_{26}BrN_3O_3$=484.4

CAS — 27848-84-6.

ATC — C04AE02.

ATC Vet — QC04AE02.

UNII — JCV8365FWN.

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

Ph. Eur. 8: (Nicergoline). A fine to granular white or yellowish powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane.

Uses and Administration

Nicergoline is an ergot derivative. It has been used similarly to codergocrine mesilate (p. 389.3) to treat symptoms of mental deterioration associated with cerebrovascular insufficiency (see Dementia, p. 388.1) and has also been used in peripheral vascular disorders (p. 1272.3). Nicergoline has been given orally in doses of up to 60 mg daily in divided doses. It has also been given by intramuscular injection and by intravenous infusion. Nicergoline tartrate has been used in parenteral dosage forms.

References.

1. Ronchi F, *et al.* Symptomatic treatment of benign prostatic obstruction with nicergoline: a placebo controlled clinical study and urodynamic evaluation. *Urol Res* 1982; 10: 131–4.
2. Bousquet J, *et al.* Double-blind, placebo-controlled study of nicergoline in the treatment of pruritus in patients receiving maintenance hemodialysis. *J Allergy Clin Immunol* 1989; 83: 825–8.
3. Saletu B, *et al.* Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: a double-blind, placebo-controlled, clinical and EEG/ERP mapping study. *Psychopharmacology (Berl)* 1995; 117: 385–95.
4. Herrmann WM, *et al.* A multicenter randomized double-blind study on the efficacy and safety of nicergoline in patients with multi-infarct dementia. *Dementia Geriatr Cogn Disord* 1997; 8: 9–17.
5. Fioravanti M, Flicker L. Nicergoline for dementia and other age associated forms of cognitive impairment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 28/04/05).
6. Felisati G, *et al.* Nicergoline in the treatment of dizziness in elderly patients: a review. *Arch Gerontol Geriatr Suppl* 2004; 163–70.
7. Winblad B, *et al.* Therapeutic use of nicergoline. *Clin Drug Investig* 2008; 28: 533–52.

Adverse Effects and Precautions

Adverse effects that may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral doses, hypotension.

Incidence of adverse effects. Adverse effects occurred in 25 of 359 patients with cerebrovascular insufficiency treated with nicergoline for 1 month;[1] the drug had to be withdrawn in 11. The reactions included 6 cases of hot flushes, 8 of general malaise, 2 of agitation, 3 of hyperacidity, 1 of nausea, 3 of diarrhoea, and 2 of dizziness and somnolence.

1. Dauverchain J. Bedeutung von Nicergolin bei der symptomatischen Behandlung des arteriellen Hochdrucks und der chronischen, zerebrovaskulären Insuffizienz. *Arzneimittelforschung* 1979; 29: 1308–10.

Interactions

For a study indicating that nicergoline enhances the cardiac depressant action of propranolol, see Ergot Derivatives, in Interactions of Beta Blockers, p. 1322.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cergodun; Sermion; *Austria*: Ergotop; Nicergin; Sermion; *Braz.*: Sermion; *Chile*: Sermion; *China*: Chen Rang (辰让); Fulutong (富路通); Jin Yi Xin (金亿新); Kai Er (凯尔); Lexilin (乐喜林); Nixo (尼舒); Sermion (思尔明); Shi Nuo Da (史诺达); Ya Run Ji (雅润基); *Cz.*: Ergotop; Sermion; *Fr.*: Sermion; *Ger.*: Ergobel; Nicergobeta†; Nicerium†; *Gr.*: Albotyl; Gustosal; Inelin; Sermion; *Hong Kong*: Cergodun; Qualigoline; Sermion; *Hung.*: Ergotop; Sermion; *India*: Cholergol; Nicerbium; *Indon.*: Serolin; *Ital.*: Sermion; *Jpn*: Sermion; *Mex.*: Sermion; *Philipp.*: Nicerbium; Sermion†; *Pol.*: Adavin; Circulat†; Nicerin; Niglostin; Nilogrin; Sermion; *Port.*: Sermion; *Rus.*: Nilogrin (Нилогрин)†; Sermion (Сермион); *Spain*: Sermion; Varson; *Switz.*: Sermion†; *Thai.*: Sergoline; Sermion; *Turk.*: Sermion; *Ukr.*: Nicerium (Ницериум); Sergolin (Серголин); Sermion (Сермион); *Venez.*: Sermion.

Multi-ingredient Preparations. *Arg.*: Sibelium Plus.

Nicotinaldehyde

3-Formylpyridine; Nicotinic Aldehyde; 3-Pyridinaldehyde; Pyridine-3-aldehyde.

3-Pyridinecarboxaldehyde.

C_6H_5NO=107.1

CAS — 500-22-1.

UNII — 840R4IDQ1T.

Profile

Nicotinaldehyde has been used topically in preparations for musculoskeletal and respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Rowalind.

Nicotine *(BAN)*

Nicotin; Nicotina; Nicotinum; Nikotiini; Nikotin; Nikotinas.

(S)-3-(1-Methylpyrrolidin-2-yl)pyridine.

$C_{10}H_{14}N_2$=162.2

CAS — 54-11-5.

ATC — N07BA01.

ATC Vet — QN07BA01; QP53AX13.

UNII — 6M3C89ZY6R.

Description. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae) (see p. 2632.2). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

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

Ph. Eur. 8: (Nicotine). A colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water; miscible with dehydrated alcohol. Store under nitrogen in airtight containers. Protect from light.

USP 36: (Nicotine). It should be stored under nitrogen at a temperature below 25 degrees. Protect from light and moisture.

Nicotine Polacrilex *(BANM, USAN)*

CAS — 96055-45-7.

ATC — N07BA01.

ATC Vet — QN07BA01.

Pharmacopoeias. In *US.*

USP 36: (Nicotine Polacrilex). A weak carboxylic cation-exchange resin prepared from methacrylic acid and divinylbenzene, in complex with nicotine. Store in airtight containers.

Nicotine Resinate *(BANM)*

Nicotine, résinate de; Nicotini Resinas; Nicotinresinat; Nikotiiniresinaatti; Nikotino rezinatas; Nikotin-resinát; Nikotin-rezinát.

ATC — N07BA01.

ATC Vet — QN07BA01.

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

Ph. Eur. 8: (Nicotine Resinate). A complex of nicotine with a weak cationic exchange resin. It may contain glycerol. A white or slightly yellowish powder. Practically insoluble in water. Store in airtight containers. Protect from light.

Nicotine Tartrate

Nicotine Bitartrate (USAN); Nicotine Bitartrate (BANM).

$C_{10}H_{14}N_2.2C_4H_6O_6.2H_2O$=498.4

CAS — 65-31-6 (anhydrous nicotine tartrate).

ATC — N07BA01.

ATC Vet — QN07BA01.

UNII — 7892ZN5G4I (anhydrous nicotine tartrate); R7M676M8YV (nicotine tartrate dihydrate).

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

Ph. Eur. 8: (Nicotine Ditartrate Dihydrate). A white or almost white powder. Soluble in water and in alcohol. A 10% solution in water has a pH of 3.0 to 3.4. Protect from light.

Uses and Administration

The main physiological action of nicotine is paralysis of all autonomic ganglia, preceded by stimulation. Centrally, small doses cause respiratory stimulation, while larger doses produce convulsions and arrest of respiration. The effects on skeletal muscle are similar to those on ganglia.

Nicotine chewing gum, transdermal patches, lozenges, sublingual tablets, nasal spray, or inhalator are used as aids for smoking cessation (p. 2570.2) and many such products are also used to reduce the amount smoked. For smoking *cessation*, treatment is usually continued for up to 3 months, then gradually withdrawn. For smoking *reduction*, it may be continued for up to 6 months, and an attempt to quit then made. If use is to be continued beyond 9 months, additional advice from a healthcare professional should be sought.

- *Chewing gum* is available in strengths of 2 mg and 4 mg; the nicotine may be present in the gum in the form of a complex with methacrylic acid polymer (nicotine

polacrilex). Individuals who smoke 20 cigarettes or less daily should start with the 2-mg strength gum chewed slowly over about 30 minutes when the urge to smoke occurs. Those who smoke over 20 cigarettes daily or require more than 15 pieces daily of the 2-mg gum should receive the 4-mg strength. Not more than 15 pieces should be used daily.

- *Sublingual tablets* containing the equivalent of 2 mg of nicotine as a β-cyclodextrin complex may be used: the recommended dose is 1 or 2 tablets sublingually every hour, increased to a maximum of 40 tablets daily if necessary. Nicotine tartrate has also been used sublingually.
- *Lozenges* containing 1, 1.5, 2, or 4 mg of nicotine (as the polacrilex or tartrate) are available. For abrupt cessation of, or temporary abstinence from smoking, the initial dose is one lozenge every 1 to 2 hours, or for gradual cessation of smoking, one lozenge whenever there is a strong urge to smoke. The usual daily dose is 8 to 12 lozenges with a maximum daily dose of 30 of the 1-mg lozenges or 15 lozenges for all higher strengths.
- Adhesive *transdermal patches* are designed to be worn for 16 or 24 hours and are available in different strengths that deliver from 5 to 25 mg during the recommended wearing time. One patch should be applied daily, on waking, to a dry, non-hairy area of skin on the hip, trunk, or upper arm, usually beginning with the highest strength or with a dose determined by the previous daily consumption of cigarettes. A different site of application should be used each day with 24 hours or more elapsing before the patch is applied to the same area of skin.
- A suggested initial dosage for a *nasal spray* containing 500 micrograms per spray is one spray administered into each nostril up to twice hourly as required up to a maximum of 80 sprays daily for the first 8 weeks and reduced gradually thereafter. Treatment for more than 3 months is not recommended.
- Nicotine *inhalator cartridges* contain nicotine 10 mg for use in an appropriate inhaler mouthpiece. The initial dose is 6 to 16 cartridges daily for up to 12 weeks and is reduced gradually over a further 4 to 12 weeks.

Nicotine has been used as a horticultural insecticide.

Alzheimer's disease. The use of nicotine as a cholinergic agonist is one of several methods being studied[1] to overcome brain cholinergic deficits in patients with Alzheimer's disease (see Dementia, p. 388.1). Preliminary studies[2,3] using nicotine patches have been of limited duration and were inconclusive. Transdermal nicotine has been used for the control of behavioural symptoms such as agitation in a small number of patients with Alzheimer's disease.[4] A systematic review[5] was unable to present any conclusions on the efficacy and safety of nicotine in Alzheimer's disease because of a lack of adequate randomised controlled studies.

1. Baldinger SL, Schroeder DJ. Nicotine therapy in patients with Alzheimer's disease. *Ann Pharmacother* 1995; 29: 314–15.
2. Wilson AL, *et al.* Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. *Pharmacol Biochem Behav* 1995; 51: 509–14.
3. Snaedal J, *et al.* The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. *Dementia* 1996; 7: 47–52.
4. Rosin RA, *et al.* Transdermal nicotine for agitation in dementia. *Am J Geriatr Psychiatry* 2001; 9: 443–4.
5. López-Arrieta JLA, Sanz FJ. Nicotine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 28/04/05).

Blepharospasm. Nicotine nasal spray was reported to be of benefit in a patient with blepharospasm (p. 2018.1) refractory to botulinum A toxin.[1] However, a subsequent study in 4 patients with blepharospasm reported no improvement with the use of nicotine nasal spray.[2]

1. Dursun SM, *et al.* Treatment of blepharospasm with nicotine nasal spray. *Lancet* 1996; 348: 60.
2. Dressler D, *et al.* Nicotine nasal spray is not reliable treatment for blepharospasm: results of a pilot study. *Mov Disord* 1998; 13: 190.

Extrapyramidal disorders. Nicotine transdermal patches have been reported to produce beneficial effects[1] in schizophrenic patients with antipsychotic-induced akathisia (p. 1049.2). Because of an apparent inverse association between smoking and Parkinson's disease (p. 889.1), transdermal nicotine patches have been investigated in the treatment of parkinsonian symptoms, but with little evidence of overall benefit.[2,3]

1. Anfang MK, Pope HG. Treatment of neuroleptic-induced akathisia with nicotine patches. *Psychopharmacology (Berl)* 1997; 134: 153–6.
2. Vieregge A, *et al.* Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* 2001; 57: 1032–5.
3. Lemay S, *et al.* Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28: 31–9.

Skin disorders. There have been anecdotal reports of nicotine producing beneficial effects in various skin disorders, including pyoderma gangrenosum,[1] and dermatitis due to fluorouracil therapy.[2]

1. Kanekura T, *et al.* Nicotine for pyoderma gangrenosum. *Lancet* 1995; 345: 1058.
2. Kingsley EC. 5-Fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med* 1994; 120: 813.

Smoking cessation. Smoking is the single most important cause of preventable illness and premature death in the UK and USA; it is estimated that around 1 in 5 deaths are due to smoking-related illnesses. The financial burden of smoking-related diseases on healthcare providers is also substantial. Many governments have undertaken initiatives to promote smoking cessation for which there is substantial evidence of a decline in the risk of disease[1] and death.[2] As the abstinence period increases, the reduced risk of disease in former smokers may even approach, although rarely does it ever equal, that of people who have never smoked.[1]

Nicotine dependence and the development of a characteristic withdrawal syndrome (see Dependence and Withdrawal, p. 2571.1) make stopping smoking very difficult. Many individuals relapse when trying to give up or need several attempts before successfully stopping. Both nonpharmacological and pharmacological treatments can improve the abstinence rate and are most effective when the two approaches are combined.[3-12]

Nonpharmacological methods include counselling, training in coping skills, and support groups; although the abstinence rate increases with the intensity of the support, even brief advice is effective in encouraging cessation.

The first-line pharmacological intervention is *nicotine replacement therapy* (NRT) which is an effective treatment for reducing the cravings associated with stopping smoking. NRT is available in several formulations: chewing gum, transdermal patches, inhalators, nasal sprays, sublingual tablets, and lozenges. A systematic review[9] of NRT found abstinence was more than doubled when compared with controls, regardless of the intensity of any additional nonpharmacological support. However, a later meta-analysis[13] concluded that most of the evidence comes from studies with behavioural support and it is unclear whether using NRT without regular contact would be as effective.

Choice of formulation is based on patient preference, tolerance, and previous treatments, if any. The transdermal patch is easiest to use and compliance is greatest with this route but local effects may be troublesome. The gum has an unpleasant taste initially and some find the chewing action difficult. The sublingual tablet may be useful for those who have difficulty chewing the gum. The nasal spray has a fast onset of action but may cause local irritation. The inhalator has the advantage of simulating cigarette smoking but may cause local irritation of the mouth and throat. The lozenge has the advantage that it can be sucked discreetly. Patients who are unable to tolerate one type of NRT may benefit from a course of an alternative NRT preparation.

Combination therapy with different types of NRT (patches with either the nasal spray, inhalator, or chewing gum) has also been tried as a means of increasing efficacy.[14,15]

NRT for smoking cessation is usually continued for about 3 months before being withdrawn. Although the manufacturers advise gradual withdrawal, others[6] have found that this offers no advantage and recommend abrupt withdrawal. NRT for smoking reduction is typically continued for longer periods. NRT has also been used long-term and may be of particular benefit in those patients who feel they would relapse if NRT was stopped or in those who have persistent withdrawal symptoms.

There has been concern over the use of NRT in patients with cardiovascular disease (see Effects on the Cardiovascular System, p. 2571.2) but clinical experience and studies have shown that NRT can be used with caution in these patients. The use of NRT in those who have suffered a recent myocardial infarction or those with severe arrhythmias or unstable angina is, however, contra-indicated as such patients have not been adequately studied.

Several other drugs have also been used to achieve abstinence from smoking.[16-18] *Bupropion* is effective and recommended by some as a first-line alternative to NRT; its action is said to be independent of its antidepressant activity. Bupropion with NRT has been used successfully. Evidence to support the use of most other antidepressants is lacking,[19] but *nortriptyline* appears to be effective and is used as a second-line drug. A study[20] found, however, that there was no advantage in combining nortriptyline with NRT. *Clonidine* is also effective but adverse effects limit its usefulness.[18] Preliminary investigations suggest that *selegiline* and *mecamylamine* may be effective.[16,18] The cannabinoid-1 receptor antagonist *rimonabant* has produced promising results in early studies,[16,17] although a systematic review[21] of 3 randomised controlled studies found the evidence to be inconclusive. A systematic review[22] of studies on the use of the oral nicotine receptor partial agonists *varenicline* and *cytisine* concluded that both drugs have a potential place in smoking cessation. Varenicline compared favourably with placebo and bupropion in helping smokers to quit, but its efficacy in preventing relapse still remains to be fully established. Like bupropion, varenicline is recommended by some as a first-line alternative to NRT. Cytisine is widely used in central and eastern Europe but the current evidence for efficacy is limited and better designed studies are required to test earlier findings. There is little or no evidence to support the efficacy of other treatments such as *silver acetate*, *lobeline*, or *anxiolytics* such as *buspirone*, and their use is not recommended. A *vaccine* for the prevention of smoking relapse is under investigation.[16,17]

1. Dresler CM, *et al.* Reversal of risk upon quitting smoking. *Lancet* 2006; 368: 348–9.
2. Vollset SE, *et al.* Smoking and deaths between 40 and 70 years of age in women and men. *Ann Intern Med* 2006; 144: 381–9.
3. Hudmon KS, Corelli RL. ASHP therapeutic position statement on the cessation of tobacco use. *Am J Health-Syst Pharm* 2009; 66: 291–307.
4. Anonymous. Nicotine replacement to aid smoking cessation. *Drug Ther Bull* 1999; 37: 52–4.
5. West R, *et al.* Smoking cessation guidelines for health professionals: an update. *Thorax* 2000; 55: 987–99.
6. Royal College of Physicians. *Nicotine addiction in Britain: a report of the Tobacco Advisory Group of the Royal College of Physicians.* London: Royal College of Physicians, 2000. Also available at: http://www.rcplondon.ac.uk/pubs/books/nicotine/index.htm (accessed 02/07/04)
7. Fiore MC, *et al.* A clinical practice guideline for treating tobacco use and dependence: a US public health service report. *JAMA* 2000; 283: 3244–54.
8. Covey LS, *et al.* Advances in non-nicotine pharmacotherapy for smoking cessation. *Drugs* 2000; 59: 17–31.
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13. Moore D, *et al.* Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. Abridged version: *BMJ* 2009; 338: 867–71. Full version: http://www.bmj.com/cgi/content/full/338/apr02_3/b1024?view=long&pmid=19342408 (accessed 17/06/10)
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15. Ebbert JO, *et al.* Combination pharmacotherapy for stopping smoking: what advantages does it offer? *Drugs* 2010; 70: 643–50.
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20. Aveyard P, *et al.* Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial. *BMJ* 2008; 336: 1223–7.
21. Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/07/08).
22. Cahill K, *et al.* Nicotine receptor partial agonists for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 28/06/07).

Spasticity. There have been anecdotal reports[1] of beneficial responses to nicotine in spastic dystonia.

1. Vaughan CJ, *et al.* Treatment of spastic dystonia with transdermal nicotine. *Lancet* 1997; 350: 565.

Tics. Tourette's syndrome (see Tics, p. 1030.1) is characterised by motor and vocal tics and behavioural disturbances. Nicotine[1-5] has been reported to be of benefit when used alone or with the more usual treatment of haloperidol in patients with Tourette's syndrome whose symptoms were not satisfactorily controlled with haloperidol alone. It is hoped that the use of transdermal nicotine patches will avoid the reported problems of compliance associated with the taste and gastrointestinal effects of nicotine gum.

1. McConville BJ, *et al.* The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency to Tourette's disorder. *Biol Psychiatry* 1992; 31: 832–40.
2. Silver AA, Sanberg PR. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome. *Lancet* 1993; 342: 182.
3. Dursun SM, *et al.* Longlasting improvement of Tourette's syndrome with transdermal nicotine. *Lancet* 1994; 344: 1577.
4. Sanberg PR, *et al.* Nicotine for the treatment of Tourette's syndrome. *Pharmacol Ther* 1997; 74: 21–5.
5. Silver AA, *et al.* Transdermal nicotine and haloperidol in Tourette's disorder: a double-blind placebo-controlled study. *J Clin Psychiatry* 2001; 62: 707–14.

Ulcerative colitis. Investigation of the use of nicotine in ulcerative colitis (see Inflammatory Bowel Disease, p. 1808.3) has been prompted by the observation that this condition is rare in smokers.[1] A systematic review[2] found that transdermal nicotine was more effective than placebo in producing remission in patients with active ulcerative

colitis, but appeared to be no more effective than standard therapy with a corticosteroid or aminosalicylate, and was associated with more adverse effects. It appears to be ineffective in maintaining disease remission.[3] Any role is likely to be limited to patients who do not respond to standard therapy and who can tolerate the adverse effects.[2] Local delivery to the colon, in the form of enemas[4-6] and oral modified-release capsules,[7] is under investigation as a means of reducing the adverse effects of nicotine.

1. Guslandi M. Nicotine treatment for ulcerative colitis. *Br J Clin Pharmacol* 1999; 48: 481–4.
2. McGrath J, *et al.* Transdermal nicotine for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/03/06).
3. Thomas GAO, *et al.* Transdermal nicotine as maintenance therapy for ulcerative colitis. *N Engl J Med* 1995; 332: 988–92.
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7. Green JT, *et al.* An oral formulation of nicotine for release and absorption in the colon: its development and pharmacokinetics. *Br J Clin Pharmacol* 1999; 48: 485–93.

Dependence and Withdrawal

Nicotine dependence is most commonly associated with cigarette smoking. It is characterised by a strong desire to continue taking the agent, a physical and psychological need for it, and a characteristic abstinence syndrome on withdrawal. Common symptoms seen on nicotine withdrawal include irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain, and insomnia. The management of smoking cessation is discussed under Uses and Administration, p. 2570.2.

Mild withdrawal symptoms have been reported from nicotine replacement preparations used to aid smoking cessation.

References.

1. Hatsukami D, *et al.* Physical dependence on nicotine gum: effect of duration of use. *Psychopharmacology (Berl)* 1993; 111: 449–56.
2. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med* 1994; 331: 123–5.
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5. Kessler DA. Nicotine addiction in young people. *N Engl J Med* 1995; 333: 186–9.
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Adverse Effects and Treatment

Nicotine is a highly toxic substance and in acute poisoning death may occur within 1 hour due to respiratory failure arising from paralysis of the muscles of respiration. The fatal oral dose of nicotine for an adult is from 40 to 60 mg.

Less severe poisoning causes initial stimulation followed by depression of the autonomic nervous system. Typical symptoms include burning of the mouth and throat, nausea and salivation, abdominal pain, vomiting, diarrhoea, dizziness, weakness, hypertension followed by hypotension, mental confusion, headache, hearing and visual disturbances, dyspnoea, faintness, convulsions, sweating, and prostration. Transient cardiac standstill or paroxysmal atrial fibrillation may occur.

Nicotine is rapidly absorbed through the skin or by inhalation as well as by ingestion, and nicotine poisoning may occur due to careless handling when it is used as a horticultural insecticide.

Prompt treatment of nicotine poisoning is essential. If contact was with the skin, contaminated clothing should be removed and the skin washed thoroughly with cold water without rubbing. If the patient has swallowed nicotine, gastric lavage and activated charcoal may be beneficial. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Apart from effects such as dizziness, headache, and gastrointestinal disturbances mentioned above, adverse effects associated with *nicotine replacement preparations* have also included cold and flu-like symptoms, palpitations, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety, irritability, somnolence, and dysmenorrhoea. Allergic reactions have been reported. Adverse effects associated with specific preparations include skin reactions with transdermal patches; nasal irritation, epistaxis, lachrymation, and sensations in the ear with the nasal spray; throat irritation with the spray, inhalator, sublingual tablets, lozenges, or chewing gum; aphthous ulceration with the inhalator, sublingual tablets, lozenges, or chewing gum; increased salivation and sometimes swelling of the tongue with chewing gum; cough, rhinitis, stomatitis, sinusitis, and dry mouth with the inhalator; and unpleasant taste with the sublingual tablets or lozenges. Excessive swallowing of nicotine released from oral replacement preparations may cause hiccups in the first few days of treatment.

References.

1. Greenland S, *et al.* A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998; 18: 297–308.
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Adverse effects of tobacco products. Chronic use of tobacco is linked to a variety of diseases. By the mid-1960s, epidemiological data established tobacco smoking as a cause of lung cancer (p. 710.2). Smoking is also associated with cancers of the larynx, mouth, cervix, bladder, pancreas, oesophagus, stomach, and kidneys, and with leukaemia.[1] Smoking is a risk factor in cardiovascular, respiratory, and peripheral and cerebral vascular diseases.[1-4] Smoking also increases the risk of developing peptic ulcer disease and may affect other gastrointestinal disorders.[2] There is also evidence that smoking tobacco products increases the risk of developing age-related macular degeneration,[5] type 2 diabetes mellitus,[6] and adenomatous polyps.[7]

Maternal smoking in pregnancy is associated with low birth-weight infants and increased risk of abortion, stillbirth, and neonatal death (see also Pregnancy under Precautions, p. 2572.1).

Passive smoking refers to inhalation of secondhand tobacco smoke or environmental tobacco smoke. Risks to health from passive exposure are lower than those from active smoking. However, studies have established passive smoking as a cause of lung cancer;[8] passive smoking is also associated with increased risk of heart disease[9] and chronic respiratory disease.[10,11] Smokeless tobacco products also carry risks to health, for example the association of cancers of the head and neck (see p. 708.1) with the use of mixtures of tobacco and areca (p. 2446.3) and probably snuff or chewing tobacco.[12,13]

1. Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; 52: 3–11.
2. Ashton H. Adverse effects of nicotine. *Adverse Drug React Bull* 1991; 149: 560–3.
3. Teo KK, *et al.* INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; 368: 647–58.
4. Patel RR, *et al.* Cigarette smoking and diffuse lung disease. *Drugs* 2008; 68: 1511–27.
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8. Lam TH. Passive smoking in perspective. *Med Toxicol Adverse Drug Exp* 1989; 4: 153–62.
9. Steenland K. Passive smoking and the risk of heart disease. *JAMA* 1992; 267: 94–9.
10. Law MR, Hackshaw AK. Environmental tobacco smoke. *Br Med Bull* 1996; 52: 22–34.
11. DiFranza JR, Lew RA. Mortality and morbidity in children associated with the use of tobacco products by other people. *Pediatrics* 1996; 97: 560–8.
12. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 93: 511–15.
13. Critchley JA, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003; 58: 435–43.

Effects on carbohydrate metabolism. Hyperinsulinaemia and insulin resistance have been associated with long-term use of nicotine gum.[1] Smoking tobacco products may increase the risk of developing type 2 diabetes mellitus (see above).

1. Eliasson B, *et al.* Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation* 1996; 94: 878–81.

Effects on the cardiovascular system. As mentioned above, nicotine from tobacco products is associated with increased risk of cardiovascular disease. It would not be surprising, therefore, if nicotine replacement preparations were also associated with cardiovascular adverse effects, and there are anecdotal reports of cardiovascular events, including myocardial infarction,[1,2] stroke,[3,4] and cerebral haematoma,[5] associated with use of such products. However, a case-control study in the general population,[6] and both cohort studies[7] and short-term placebo-controlled studies[8,9] in patients with cardiovascular disease have failed to show any increased cardiovascular risk associated with transdermal nicotine. Results from a retrospective matched cohort study[10] of the use of nicotine replacement therapy (NRT) in patients immediately after coronary artery bypass graft (CABG) surgery showed an increase in mortality compared with CABG-patients who did not receive NRT. The authors suggest that NRT in critically ill patients should be restricted to use after patient discharge from hospital until data on inpatient usage are available from larger studies.

1. Warner JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994; 120: 695.
2. Arnaot MR. Nicotine patches may not be safe. *BMJ* 1995; 310: 663–4.
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4. Ang R, *et al.* Nicotine replacement therapy and ischaemic stroke. *Hosp Med* 2005; 66: 366–7.
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9. Joseph AM, *et al.* The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; 335: 1792–8.
10. Paciullo CA, *et al.* Impact of nicotine replacement therapy on postoperative mortality following coronary artery bypass graft surgery. *Ann Pharmacother* 2009; 43: 1197–1202.

Vasculitis. Vasculitis occurring in 2 patients was associated with transdermal nicotine patches.[1]

1. van der Klauw MM, *et al.* Vasculitis attributed to the nicotine patch (Nicotinell). *Br J Dermatol* 1996; 134: 361–4.

Precautions

Nicotine preparations should not be used in patients who have had recent cerebrovascular accident. They should be used with caution in patients with cardiovascular disease. Use should preferably be avoided completely in severe cardiovascular disease, including during the immediate postmyocardial infarction period, and in patients with severe arrhythmias or unstable angina pectoris, although use under medical supervision may be considered if the patient is otherwise unable to stop smoking. They should be used with caution in those with peripheral vascular disease, in endocrine disorders including phaeochromocytoma, hyperthyroidism, and diabetes mellitus, in peptic ulcer disease, or renal or hepatic impairment. They should also be used with caution, and avoided if possible, during pregnancy or breast feeding (see p. 2572.1 and below, respectively).

Skin patches should not be used on broken skin.

Breast feeding. The American Academy of Pediatrics[1] notes that there have been reports of decreased milk production in breast-feeding mothers who smoke, and of decreased weight gain in the infant. There is, however, controversy regarding the effects of nicotine on infant size at 1 year of age. Although nicotine and its metabolite cotinine have been shown to be distributed into breast milk there are hundreds of compounds in tobacco smoke; nicotine is not necessarily the only component that might be detrimental to the breast-fed infant. Nicotine is present in breast milk in concentrations between 1.5 to 3 times the maternal plasma concentration, but there is no evidence documenting whether this amount of nicotine presents a health risk to the infant. Indeed, one study reported that the incidence of acute respiratory illness in infants whose mothers smoked was decreased in those who were breast fed when compared with those infants who were bottle fed.

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 02/07/04)

Exercise. Physical exercise increased mean peak plasma concentrations of nicotine in 8 healthy subjects treated with a transdermal nicotine patch.[1] The effect was thought to be most likely due to increased skin perfusion resulting in increased uptake.

1. Klemsdal TO, *et al.* Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. *Br J Clin Pharmacol* 1995; 39: 677–9.

Myasthenia gravis. A patient with myasthenia gravis noted worsening of his symptoms after application of transdermal nicotine patches, the effects being most severe about 1 hour after application, and resolving within 3 hours once the patch was removed.[1] Previous heavy smoking had not produced similar adverse effects, despite the fact that blood-nicotine concentrations are typically higher just after finishing a cigarette than when using the patch.[2]

1. Moreau T, *et al.* Nicotine-sensitive myasthenia gravis. *Lancet* 1994; 344: 548–9.
2. Pethica D. Nicotine-sensitive myasthenia gravis. *Lancet* 1994; 344: 961.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nicotine-contain-

ing products (used as aids for smoking cessation) as probably 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 01/11/11)

Pregnancy. Cigarette smoking during pregnancy is associated with an increased risk of low birth-weight, spontaneous abortion, and perinatal mortality.[1] There is also some evidence of a possible association between smoking during pregnancy and the sudden infant death syndrome (SIDS).[2] In addition to nicotine, cigarette smoke contains many other chemicals, which are also fetal toxins, including carbon monoxide and lead.[3] Results from a study[4] in a large community sample showed that exposure to maternal smoking was associated with increased irritability and hypertonicity in neonates. Although smoking poses a far greater risk than pure nicotine, nicotine replacement therapy (NRT) is not without potential risks and should be reserved for mothers unable to quit with behavioural therapy alone.[3] It has been suggested that where NRT is required, the intermittent delivery formulations such as nicotine gum or inhalator, which expose the fetus to a lower total dose of nicotine, are preferable to continuous use formulations such as patches.[3]

1. British Medical Association. *Smoking and reproductive life: the impact of smoking on sexual, reproductive and child health.* London: British Medical Association, 2004. Available at: http://www.bma.org.uk/images/smoking_tcm41-21289.pdf (accessed 16/06/10)
2. Wisborg K, *et al.* A prospective study of smoking during pregnancy and SIDS. *Arch Dis Child* 2000; **83**: 203–6. Corrections. *ibid.* 2001; **84**: 93 and 187.
3. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; **24**: 277–322.
4. Stroud LR, *et al.* Maternal smoking during pregnancy and neonatal behavior: a large-scale community study. Abstract: *Pediatrics* 2009; **123**: 1398–9. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/5/e842 (accessed 16/06/10)

Interactions

Tobacco smoking induces hepatic metabolic enzymes and the pharmacokinetics of many drugs are altered. Drugs such as methoxsalen which inhibit the cytochrome P450 isoenzyme CYP2A6 may decrease the metabolism of nicotine, resulting in increased plasma concentrations.

References.

1. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9**: 125–35.
2. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36**: 425–38.
3. Sellers EM, *et al.* Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clin Pharmacol Ther* 2000; **68**: 35–43.
4. Hukkanen J, *et al.* Effects of nicotine on cytochrome P450 2A6 and 2E1 activities. *Br J Clin Pharmacol* 2010; **69**: 152–9.

Interactions with tobacco smoking. For reports of possible interactions between tobacco smoking and some drugs, see:

- antipsychotics (see Chlorpromazine, p. 1053.2)
- atracurium, p. 2033.2
- benzodiazepines (see Diazepam, p. 1070.3)
- bupropion, see under Pharmacokinetics, p. 410.3
- corticosteroids, p. 1620.3
- fluvoxamine (see under Fluoxetine, p. 425.1)
- insulin, p. 486.2
- irinotecan, p. 814.2
- lidocaine, p. 1991.1
- melatonin, p. 2552.2
- pentazocine, p. 121.2
- quinine, p. 668.2
- theophylline, p. 1233.3
- tricyclic antidepressants (see Amitriptyline, p. 407.2)
- vecuronium, p. 2033.2

Nicotinic acid. As described on p. 2084.3, a possible interaction between nicotinic acid and nicotine from a transdermal patch has been reported.

Pharmacokinetics

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first-pass metabolism. Nicotine is widely distributed; it crosses the blood-brain barrier and the placenta and is found in breast milk. The elimination half-life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotinine and nicotine-*N*-oxide. Nicotine and its metabolites are excreted in the urine.

References.

1. Gorsline J, *et al.* Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm (nicotine transdermal system). *J Clin Pharmacol* 1993; **33**: 161–8.
2. Gupta SK, *et al.* Bioavailability and absorption kinetics of nicotine following application of a transdermal system. *Br J Clin Pharmacol* 1993; **36**: 221–7.
3. Schneider NG, *et al.* Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 1996; **31**: 65–80.
4. Benowitz NL, *et al.* Sources of variability in nicotine and cotinine levels with the use of nicotine nasal spray, transdermal nicotine and cigarette smoking. *Br J Clin Pharmacol* 1997; **43**: 259–67.
5. Zins BJ, *et al.* Pharmacokinetics of nicotine tartrate after single-dose liquid enema, oral, and intravenous administration. *J Clin Pharmacol* 1997; **37**: 426–36.
6. Schneider NG, *et al.* The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001; **40**: 661–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nicorette; Nicotinell TTS; NiQuitin; Niux; *Austral.*: Nicabate; Nicorette; Nicotinell; QuitX; *Austria*: Nicorette; Nicotinell; Nicotrol; NiQuitin; *Belg.*: Nicopatch; Nicorette; Nicotinell; NiQuitin; *Braz.*: Nicorette; Nicotinell TTS; NiQuitin; *Canad.*: Habitrol; Nicoderm; Nicorette; Nicotrol†; Prostep†; Thrive; *Chile*: Nicorette; Nicotinell; *China*: Ao Fei Ni (奥菲尼); Nicorette (力克雷); Nicotinell (尼古丁); NiQuitin (力凯定); *Cz.*: Nicopass†; Nicopatch†; Nicorette; Nicotinell†; NiQuitin; *Denm.*: Nicodose; Nicorette; Nicotinell; Nicovel; Nikaloz; Zonnic; *Fin.*: Nicopass; Nicopatch; Nicorette; Nicotinell; Nicotrol†; *Fr.*: Nicogum†; Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; NiQuitinminis; *Ger.*: Nicorette; Nicotinell†; nikofrenon; NiQuitin; *Gr.*: Camryn; Exodus; Nicopass; Nicopatch; Nicorette; Nicotinell; *Hong Kong*: Nicorette; Nicotinell; *Hung.*: Nicopass†; Nicorette; Nicotinell; NiQuitin; *India*: Nicotex-2; Nullfe; *Irl.*: Boots NicAssist; NCH; Nicopass; Nicorette; Nicotinell; NiQuitin; *Israel*: Nicorette; Nicotinell; NiQuitin†; *Ital.*: Nicorette; Nicotinell; NiQuitin; *Malaysia*: Nicorette; Nicotinell; NiQuitin; *Mex.*: Nicorette; NiQuitin; *Neth.*: Exmo; Nicopass; Nicopatch†; Nicorette; Nicorol; Nicotinell; Niqero; NiQuitin; *Norw.*: Nicorette; Nicotinell; Nicovel; *NZ*: Habitrol; Nicabate†; Nicorette; Nicotinell; Nicotrol; *Philipp.*: Nicorette; Nicotinell; *Pol.*: Nicorette; Nicotinell†; NiQuitin; *Port.*: Nicopass; Nicopatch; Nicorette; Nicotinell; NiQuitin; *Rus.*: Nicorette (Никоретте); Nicotinell (Никотинелл); NiQuitin (НиКвитин); *S.Afr.*: Nicorette; Quit; *Singapore*: Nicorette; Nicotinell; Niquitin; *Spain*: Nicorette; Nicotinell; NiQuitin; *Swed.*: Nicorette; Nicotinell; Nikotugg†; NiQuitin; Zonnic; *Switz.*: Nicorette; Nicotinell; *Thai.*: Nicomild; Nicorette; Nicotinell; *Turk.*: Nicotinell; *UK*: Nicopass†; Nicopatch†; Nicorette; Nicotinell; NiQuitin; *Ukr.*: Nicorette (Никоретте); *USA*: Commit†; Habitrol; Nicoderm; NicoRelief; Nicorette; Nicotrol; Prostep; Thrive.

Homoeopathic Preparations. *Canad.*: Nixotinex.

Pharmacopoeial Preparations

BP 2014: Nicotine Inhalation Cartridges; Nicotine Nasal Spray; Nicotine Resinate Medicated Chewing Gum; Nicotine Sublingual Tablets; Nicotine Transdermal Patches;

USP 36: Nicotine Polacrilex Gum; Nicotine Transdermal System.

Nitisinone *(USAN, rINN)*

Nitisinona; Nitisinonum; NTBC; SC-0735; Нитизинон.

2-(α,α,α-Trifluoro-2-nitro-*p*-toluoyl)-1,3-cyclohexanedione.

$C_{14}H_{10}F_3NO_5$=329.2

CAS — 104206-65-7.

ATC — A16AX04.

ATC Vet — QA16AX04.

UNII — K5BN214699.

Uses and Administration

Nitisinone is a 4-hydroxyphenylpyruvate dioxygenase inhibitor used in the management of hereditary tyrosinaemia type 1; dietary restriction of tyrosine and phenylalanine is also necessary. An initial daily dose of 1 mg/kg given orally is recommended; daily dosage should be given in 2 divided doses, which may be unequally split. Monitoring of urine succinylacetone and plasma alpha-fetoprotein, as well as liver function tests, must be carried out. If necessary, the daily dose may be increased to 1.5 mg/kg after one month; the maximum daily dose is 2 mg/kg. If satisfactory results are obtained from biochemical testing, doses should only be increased in line with body-weight gain.

Nitisinone is under investigation for the treatment of alkaptonuria, another hereditary metabolic disorder.

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2. Phornphutkul C, *et al.* Natural history of alkaptonuria. *N Engl J Med* 2002; **347**: 2111–21.
3. Gissen P, *et al.* Ophthalmic follow-up of patients with tyrosinaemia type I on NTBC. *J Inherit Metab Dis* 2003; **26**: 13–16.
4. Joshi SN, Venugopalan P. Experience with NTBC therapy in hereditary tyrosinaemia type I: an alternative to liver transplantation. *Ann Trop Paediatr* 2004; **24**: 259–63.
5. Suwannarat P, *et al.* Use of nitisinone in patients with alkaptonuria. *Metabolism* 2005; **54**: 719–28.
6. McKlerman PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. *Drugs* 2006; **66**: 743–50.

Adverse Effects and Precautions

Adverse effects of nitisinone have included granulocytopenia, leucopenia, and thrombocytopenia; regular monitoring of platelet and white cell counts is recommended. Eye disorders may occur due to increases in plasma tyrosine; they include conjunctivitis, corneal opacity, keratitis, photophobia, and eye pain. Slit-lamp examination of the eyes is recommended before starting treatment; patients developing visual disturbances during treatment should be referred to an ophthalmologist immediately, and further dietary restrictions implemented if plasma tyrosine is too high. Although it is unknown if nitisinone is excreted into human milk, breast feeding is contra-indicated because of the potential effects on a suckling child.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Orfadin; Orfadin; *Belg.*: Orfadin; *Cz.*: Orfadin; *Denm.*: Orfadin; *Fin.*: Orfadin; *Fr.*: Orfadin; *Ger.*: Orfadin; *Gr.*: Orfadin; *Irl.*: Orfadin; *Israel*: Orfadin; *Neth.*: Orfadin; *Norw.*: Orfadin; *Pol.*: Orfadin; *Port.*: Orfadin; *Rus.*: Orfadin (Орфадин); *Spain*: Orfadin; *Swed.*: Orfadin; *USA*: Orfadin.

Nitric Acid

Acide nitrique; Acidum Nitricum; Acidum Nitricum 70%; Aqua Fortis; Azotic Acid; Kwas azotowy; Kyselina dusičná 70%; Nit. Acid; Nitrato rūgštis; Nítrico, ácido; Salétromsav; Salpetersäure; Salpetersyra; Typpihappo.

HNO_3=63.01

CAS — 7697-37-2.

UNII — 411VRN1TV4.

Pharmacopoeias. In *Eur.* (see p. vii) (68 to 70%). Also in *USNF* (69 to 71%).

Ph. Eur. 8: (Nitric Acid). A clear, colourless to almost colourless liquid. Miscible with water. It contains 68.0 to 70.0% w/w of HNO_3. Protect from light.

USNF 31: (Nitric Acid). A highly corrosive fuming liquid, having a characteristic, highly irritating odour. It contains 69.0 to 71.0% w/w of HNO_3. Store in airtight containers.

Uses and Administration

Nitric acid has a powerful corrosive action and has been used to remove warts (p. 1689.3), but it should be applied with caution, and less corrosive substances are available. It has also been used for the removal of tattoos.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

There may be methaemoglobinaemia. Nitric acid stains the skin yellow.

Effects on the respiratory system. Respiratory failure due to pulmonary oedema occurred in a 56-year-old man after inhaling nitric acid which he had used as a metal cleaner.[1] The man died despite extensive ventilatory support.

1. Bur A, *et al.* Fatal pulmonary edema after nitric acid inhalation. *Resuscitation* 1997; **35**: 33–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: Solcoderm (思可得); *Ger.*: Solco-Derman; *Hong Kong*: Solcoderm†; *Pol.*: Solcogyn; *Rus.*: Solcoderm (Солкодерм); Solcovagin (Солковагин); *Switz.*: Solcoderm; Solcogyn; *Ukr.*: Solcoderm (Солкодерм); Solcovagin (Солковагин).

Homoeopathic Preparations. *Austria*: Argentum Med Complex; Erbiode Blasen und Nieren; *Canad.*: Bioactiv H†; Cat Complex†; Detox L37; Echinacea L40†; Homeo-Form PMT†; PMS; Reneel†; Renelix; War Complex†; *Chile*: Bioactiv H; *Cz.*: Galium; Hormeel S; Lamioflur†; *Fr.*: Cimicifuga Complexe No 21†; Echinacea Complexe No 40; Euphorbium Complexe No 88; Juniperus Complexe No 6; Mercurius Cyanatus Complexe No 43†; Rhododendron Complexe No 42†; Thuya Complexe No 37; Verrulia; *Ger.*: Haemorrhoid-Gastreu N; Lowe-Komplex Nr 6; Onocalman; Regenaplex Haut W; Rufebran gastro†; Solidago Hevert Complex; Ulco-cyl L Ho-Len-Complex; *Hung.*: Hormeel S; *Neth.*: Akutur spag; Habifac; Opsonat; *Rus.*: Helidonium-Plus (Хелидониум-Плюс); Hormeel SN (Гормель СН); Paeonia-Plus (Пеония-Плюс); *Switz.*: Regenaplex Nr 28a; Regenaplex Nr 86a; Regenaplex Nr. 25b; Regenaplex Nr. 25c; Regenaplex Nr. 31a; Regenaplex Nr. 50b; Regenaplex Nr. 59b; Regenaplex Nr. 71b.

Pharmacopoeial Preparations

USP 36: Ferric Subsulfate Solution.

Nitrobenzene

Aceite de mirbana; Nitrobenceno; Nitrobenzen; Nitrobenzol; Oil of Mirbane.

$C_6H_5NO_2$=123.1

CAS — 98-95-3.
UNII — E57JCN6SSY.

Uses

Nitrobenzene is used in the manufacture of aniline, as a preservative in polishes, and in perfumery and soaps.

Adverse Effects

Nitrobenzene is highly toxic and the ingestion of 1 g may be fatal. Poisoning may occur from absorption through the skin, by inhalation, or by ingestion. Toxic effects are usually delayed for several hours and may include nausea, prostration, burning headache, methaemoglobinaemia with cyanosis, haemolytic anaemia, vomiting (with characteristic odour), convulsions, and coma, ending in death after a few hours.

Treatment of Adverse Effects

Although the benefit of gastric decontamination after ingestion of nitrobenzene is uncertain, gastric lavage or activated charcoal may be considered if given within 1 hour of ingestion. Methaemoglobinaemia may be treated with methylthioninium chloride. Oxygen should be given if cyanosis is severe.

If the skin or eyes are splashed with nitrobenzene, contaminated clothing should be removed immediately and the affected areas washed thoroughly with water at room temperature for at least 15 minutes.

Nix-0699

NOTE. The names Hemoxin, Nicosan, and Niprosan have been used as trade marks for nix-0699.

Profile

Nix-0699 is an extract of the leaf of *Sorghum bicolor* (sorghum), the stem of *Pterocarpus osun* (camwood), the seed of *Piper guineense* (Ashanti or Benin pepper), and the flower of *Syzygium aromaticum*; *Eugenia caryophyllus* (clove). It is being investigated in the treatment of sickle-cell disease.

Reviews.

1. Cordeiro NJV, Oniyangi O. Phytomedicines (medicines derived from plants) for sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 19/08/08).

Nucleic Acid

Acide Zymonucléique; Acidum Nucleicum; Nucleico, ácido; Nucleinic Acid; Нуклеиновая Кислота.

Profile

Nucleic acids, which are present in all cellular organisms and viruses, are composed of high molecular weight polynucleotides. A nucleotide is a phosphate ester of a nucleoside, which is made up of either a purine or pyrimidine nitrogenous base attached to a pentose sugar by an *N*-glycosidic linkage. Diester phosphate linkages between the sugar moieties produce a polynucleotide strand. Nucleic acids are of two types: deoxyribonucleic acid (DNA) (p. 2492.2) and ribonucleic acid (RNA) (p. 2604.1). Synthetic or recombinant nucleic acids are used in gene therapy (p. 2511.2).

Since the administration of nucleic acid gives rise to a marked temporary leucocytosis (usually preceded by a short period of leucopenia) it was formerly given in the treatment of a variety of bacterial infections in the hope of enhancing the natural defence mechanisms. Its therapeutic value, however, has never been established.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Nulip†.

Nutmeg

Muscade; Myristica; Noz Moscada; Nuez Moscada; Nux Moschata; Мускатный Орех.
ATC Herb. — HN02BG5009 (Myristica fragrans: seed); HA07XA5006 (Myristica fragrans: seed); HN05CM5016 (Myristica fragrans: seed); HA03AW5041 (Myristica fragrans: seed).
UNII — AEE24M3MQ9.

Description. Nutmeg consists of the dried kernels of the seeds of *Myristica fragrans* (Myristicaceae), containing not less than 5% v/w of volatile oil; the powdered drug contains not less than 4% v/w. Mace (see Mace Oil, p. 2547.3) is the dried arillus of the seed of *M. fragrans*.

Pharmacopoeias. In *Chin*.

Uses and Administration

Nutmeg is the source of nutmeg oil (below). It is aromatic and carminative and is used as a flavour. Nutmeg has been reported to inhibit prostaglandin synthesis.

Homoeopathy

Nutmeg has been used in homoeopathic medicines under the following names: Myristica fragrans; Nux moschata; Nux mosch; Nux. mos.

References.

1. Barceloux DG. Nutmeg (*Myristica fragrans* Houtt.). *Dis Mon* 2009; **55**: 373–9.

Adverse Effects

Nutmeg, taken in large doses, may cause nausea and vomiting, flushing, dry mouth, tachycardia, stimulation of the CNS possibly with epileptiform convulsions, miosis or occasionally mydriasis, euphoria, and hallucinations. Myristicin and elimicin are thought to be the constituents responsible for the psychotic effects of nutmeg, possibly because of metabolism to amfetamine-like compounds.

Some references to the adverse effects of nutmeg.

1. Panayotopoulos DJ, Chisholm DD. Hallucinogenic effect of nutmeg. *BMJ* 1970; **1**: 754.
2. Brenner N, *et al.* Chronic nutmeg psychosis. *J R Soc Med* 1993; **86**: 179–80.
3. Sangalli BC, Chiang W. Toxicology of nutmeg abuse. *J Toxicol Clin Toxicol* 2000; **38**: 671–8.
4. Stein U, *et al.* Nutmeg (myristicin) poisoning—report on a fatal case and a series of cases recorded by a poison information centre. *Forensic Sci Int* 2001; **118**: 87–90.
5. Kelly BD, *et al.* Nutmeg and psychosis. *Schizophr Res* 2003; **60**: 95–6.
6. McKenna A, *et al.* Acute nutmeg poisoning. *Eur J Emerg Med* 2004; **11**: 240–1.
7. Demetriades AK, *et al.* Low cost, high risk: accidental nutmeg intoxication. *Emerg Med J* 2005; **22**: 223–5.
8. Forrester MB. Nutmeg intoxication in Texas, 1998-2004. *Hum Exp Toxicol* 2005; **24**: 563–6.
9. Pérez Valdivieso JR. Intoxicación aguda por nuez moscada. *Rev Esp Anestesiol Reanim* 2007; **54**: 633–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Klosterfrau Melissengeist; Mariazeller; Pervivo; *Belg.*: Eau Des Carmes; *Braz.*: Paratonico†; Vitonico; *Cz.*: Dr Theiss Schwedenbitter†; Klosterfrau Melisana; Original Schwedenbitter; *Ger.*: Klosterfrau Melissengeist; Melissengeist; *Hung.*: Bano Svedkeseru; Bittner; Klosterfrau Melisana; *India*: Diakol; Koflet; Laviril; Lukol; Mentat; Mustong; *Pol.*: Melisana Klosterfrau; Pervivo; *Rus.*: Doppelherz Melissa (Доппельгерц Мелисса); Fitovit (Фитовит); Himcolin (Химколин); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Entressdruppels HM; Melissengeist†; Rooilavental; Spiritus Contra Tussim Drops†; *Spain*: Agua del Carmen; *UK*: Digestion Calming Drops; Melissa Comp.; *Ukr.*: Bronchomed (Бронхомед); Fitovit (Фитовит); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trypsidan (Трипсидан)†.

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; Relax; *Canad.*: Homeogene 46; Hylands Gas; *Cz.*: Hepeel; Hormeel S; *Fr.*: Eudyne†; Homeogene 46; *Ger.*: Neuri-cyl N Ho-Len-Complex; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Ryteshin; Sedaphin†; Tamechol; *Hung.*: Hepeel; Hormeel S; *Neth.*: Speci-chol; *Rus.*: Hormeel SN (Гормель СН); *Switz.*: Hepeel; *UK*: Cough Drops.

Nutmeg Oil

Ätherisches Muskatöl; Esencia de Nuez Moscada; Essence de Muscade; Essência de Moscada; Muskatų eterinis aliejus; Muskatöl; Muškátovníková silice; Muskotolja; Muskottiöljy; Myristica Oil; Myristicae Etheroleum; Myristicae Fragrantis Aetheroleum; Noix muscade, huile essentielle de; Nuez moscada, aceite esencial de; Oleum Myristicae; Szerecsendióolaj; Эфирное Масло Мускатного Ореха.
UNII — Z1CLM48948.

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

Ph. Eur. 8: (Nutmeg Oil). The oil obtained by steam distillation of the dried and crushed kernels of *Myristica fragrans*. A colourless to pale yellow liquid with a spicy odour. Store in well-filled, airtight containers. Protect from light and heat.

Profile

Nutmeg oil is aromatic and carminative and is used as a flavour. Nutmeg oil and expressed nutmeg oil, a solid fat, are rubefacient. Nutmeg oil is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Vicks Vaporub; *Austria*: Pe-Ce†; *Belg.*: Vicks Vaporub; *Braz.*: Vick Vaporub; *Canad.*: Melisana†; Vaporizing Ointment†; *Chile*: Agua Melisa Carminativa; *Fr.*: Activox; Aromadetox†; Aromadigest†; Aromavital†; Vicks Vaporub; *Ger.*: esto-gast; *Gr.*: EKS; Revigel; *Hung.*: Carmol; Kinder Luuf Balsam; *NZ*: Vicks Vaporub; *Pol.*: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Wick Vaporub; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Doktor Mom (Доктор Мом); *S.Afr.*: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Enterodyne†; Stuidruppels; Vicks Vaporub†; *Spain*: Arkoresp†; *Swed.*: Vicks Vaporub; *Switz.*: Eucapinol; Vicks Vaporub N; *Turk.*: Vicks Vaporub; *UK*: Dragon Balm; No-Sor Vapour Rub; Nowax; *Ukr.*: Doktor Mom (Доктор Мом); Rostiran (Ростиран); *USA*: Vicks Vaporub.

Pharmacopoeial Preparations
BP 2014: Aromatic Ammonia Spirit.

Nux Vomica

Brechnuss; Noce Vomica; Noix Vomique; Nuez vómica; Strychni Semen; Чилибуха.
CAS — 357-57-3 (anhydrous brucine).
ATC Herb. — HA15WA5001 (Strychnos nux-vomica: seed); HA13AW5001 (Strychnos nux-vomica: seed).
UNII — 269XH13919.

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Nux vomica consists of the dried ripe seeds of *Strychnos nux-vomica* (Loganiaceae). It has the actions of strychnine (see p. 2623.2). As well as containing strychnine, nux vomica contains brucine which has similar properties.

Nux vomica is used in herbal medicine for several disorders including those of digestion or debility.

Homoeopathy

Nux vomica has been used in homoeopathic medicines under the following names: Nux vom.; Strychnos nux-vomica.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Mindac; Nervatona Calm; Nervatona Focus; *Braz.*: Gotas Digestivas; *Chile*: Fenokomp 39; *India*: Arthrill; *Mex.*: Bigenol†; *Philipp.*: BSI Medicated Spray; *Port.*: Cephyl†; *Rus.*: Tentex (Тентекс); *Spain*: Alofedina; *Switz.*: Padma-Lax; Padmed Laxan; *Thai.*: Corisul; Flataco; Flatulence†; Patarsul.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Elimitona Slim & Detox; Elimitona; Hangover Relief; IBS Eze; Nervatona Calm; Nervatona Focus; Respatona Head Cold; Respatona Nasal Spray Decongestant; Snore Eze; Snorestop; Stomach Calm; Teething Relief; Travellers Relief; *Austria*: Argentum Med Complex; Astomera; Gastricumeel; Katerex; Nux Med Complex; Nux Vomica-Homaccord; Schnarchex; Vomitusheel; *Canad.*: Acne; Hylands Hemorrhoids; Hylands Motion Sickness; Hylands Upset Stomach; Kids Allergies; Passiflora Complex†; *Chile*: Bioactiv S; Bioactiv V; *Cz.*: Cocculine; Gastrocynesine; *Fr.*: Abbe Chaupitre no 15†; Abbe Chaupitre no 18†; Abbe Chaupitre no 30†; Abbe Chaupitre no 82†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Aesculus Complexe No 103; Arnica Complexe no 1; Boripharm No 15†; Boripharm No 1†; Carominthe; Cholesterolum Complexe No 112†; Cocculine; Cocculus Complexe No 73; Crataegus Complexe No 15; Dolisedal†; Gastro-Drainol†; Gastrocynesine; Gelsemium Complexe No 70; Gentiana Complexe No 33†; Grindelia Complexe No 58; Homeogene 21†; L 107; L 114; Millefolium Complexe No 7†; Momordica Complexe No 109†; Nausetum; Nux Vomica Complexe No 49; Nux Vomica Compose; Oenanthe Crocata Complexe No 78; Polyrhinium; Rhododendron Complexe No 42†; Rhus Toxicodendron Complexe No 80; Soreal; Tabapass; Tamarindus Complexe No 95†; Tonique Vegetal; Veinosium†; Vinicard†; Yucca Complexe No 110; *Ger.*: Arnica Oligoplex; Berberis N Oligoplex; Biodolor; Bomagall; Carminativum Hevert; Choanol N; Colintest-Gastreu; Femi-cyl L Ho-Len-Complex; gastri-loges N; Gastriselect N; Gastro Magentabletten; Gastro-Pasc; Gelsemium Comp; Gripps; Haemorrhoid-Gastreu N; Hepa-Gastreu N R7; Heparanox H; Infi-China; Infifer N; Infinerval; Influvit; Jowidamin; Jsostoma S; Leber Albin; Leber-Galletropfen; Lowe-Komplex Nr 6; Metaharonga; Mucosa compositum; Nervo-Plantin†; Nuvorell; Nux Vomica N Oligoplex; Nuxal comp; Nuxal H; Pflugerplex Gelsemium; Rheuma-Hevert; Rheuma-Hevert; Rheumaselect; Schwoneural N; Spasmo-Bomaleb†; Ventrigutt M; Vertigo-Hevert; *Hung.*: Cocculine; *Neth.*: Ambheel; Apo-STOM; Cocculine; Colintest-Gastreu R37; Collite; Cystilite; Gastricumeel; Gastrifleur; Gastrocynesine†; Gravifem†; Hepa-Gastreu R7; Hepeel H; Homeocare Digesto; Homeocare Vasco; Mucosa comp H; Nux Vomica-Homaccord; Rhodolith-Gastreu R46; Snurdim; Travelin; *Port.*: Cocculine; Gastrocynesine; *Rus.*: Berberis-Plus (Берберис-Плюс); Capsicum-Plus (Капсикум-Плюс); Cocculine (Коккулин); Helido-

The symbol † denotes a preparation no longer actively marketed

nium-Plus (Хелидониум-Плюс); Nux Vom-Plus (Нукс Вом-Плюс); *Switz.*: Cocculine; Gastricumeel; Gastronol; HerBalance; Lithiumeel; Nelsons Travella†; Polyrhinium; Regenaplex Nr. 12; Regenaplex Nr. 24c; Regenaplex Nr. 25a; Regenaplex Nr. 25b; Regenaplex Nr. 59b; Vomitusheel; *UK*: Nausyn; Travella; *USA*: Preferred Remedies Aches & Pains; Preferred Remedies Antacid; Preferred Remedies Detoxin.

Oak Bark

Chêne, écorce de; Common Oak; Corteza de roble; Dubová kůra; Durmast Oak; Écorce de Chêne; Eichenrinde; Ekbark; Kora dębowa; Quercus; Quercus cortex; Tammenkuori; Tölgyfakéreg; Ąžuolų žievė; Дубовая Кора.

ATC Herb — HD03WA5008 (Quercus robur: *bark*); *HA07XA5009* (Quercus petraea: *bark*); *HD03WA5007* (Quercus petraea: *bark*); *HA01WA5005* (Quercus petraea: *bark*); *HA01WA5006* (Quercus robur: *bark*); *HA07XA5010* (Quercus robur: *bark*).

UNII — 2JFK226947 (Quercus robur *twig bark*); *ML644HED2V* (Quercus robur *flower*); *Q7MU1F4GLY* (Quercus robur *nut*).

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

Ph. Eur. 8: (Oak Bark). The cut and dried bark from the fresh young branches of *Quercus robur*, *Q. petraea*, and *Q. pubescens*. It contains a minimum of 3.0% of tannins, expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Oak bark contains quercitannic acid. It has astringent properties and is used in some herbal preparations. It was formerly used for haemorrhoids and as a gargle.

Homoeopathy

Oak bark has been used in homoeopathic medicines under the following names: Quercus; Quercus robur; Quercus rob.

The flowers of *Quercus robur* are used in homoeopathic medicines under the following names: Quercus robur, flos; Quercus rob, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Urocalun (优克龙); *Cz.*: Dubova Kura†; *Hong Kong*: Urocalun†; *Jpn*: Urocalun; *Pol.*: Quecor; *Singapore*: Urocalun; *USA*: Amerigel.

Multi-ingredient Preparations. *Austria*: Menodoron; *Ger.*: Imupret; Menodoron; *Hung.*: Gombarex; *India*: Acneguard; *Jpn*: Jidabokuippo; Jumihaidokuto; *Pol.*: Arnisol; Dentosept A; Dentosept; Enterosol; Mucosit; Sanofil; Stomatosol; *Rus.*: Polygemostat (Полигемостат); Stomatophit (Стоматофит); Tonsilgon N (Тонзилгон Н); *S.Afr.*: Menodoron†; *Switz.*: Kernosan Eau Dentifrice†; Kernosan Elixir; Menodoron; *UK*: Peerless Composition Essence; *Ukr.*: Imupret (Имупрет); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Tonsilgon N (Тонзилгон)†; *USA*: Amerigel.

Homoeopathic Preparations. *Canad.*: Homeodel 15†; *Fr.*: Gentiana Complexe No 33†; Sels Calcaires Nutritifs; *Ger.*: Lobelia comp; *S.Afr.*: Aufbaukalk II†; *UK*: Conchae comp..

Ocriplasmin *(USAN, rINN)*

Microplasmin; Ocriplasmina; Ocriplasmine; Ocriplasminum; Окриплазмин.

Truncated human plasmin: human plasmin heavy chain A-(543-561)-peptide (548-666;558-566)-bisdisulfide with human plasmin light chain B.

CAS — 1048016-09-6.

UNII — 7V6HE3DM5A.

Profile

Ocriplasmin is a recombinant proteolytic enzyme used in the treatment of symptomatic vitreomacular adhesion.

It is given by intravitreal injection into the affected eye in a single dose of 125 micrograms. Repeated injection of ocriplasmin in the same eye is not recommended. Treatment of the other eye, if required, is not recommended within 7 days of the initial injection, to allow monitoring for adverse effects in the injected eye.

Reported adverse effects include vitreous floaters, conjunctival haemorrhage, eye pain, photopsia, dyschromatopsia, and decreased visual acuity.

References.

1. Stalmans P, *et al.* MIVI-TRUST Study Group. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. *N Engl J Med* 2012; 367: 606–15. Correction. *ibid.*: 2054.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Jetrea; *USA*: Jetrea.

Octamylamine *(rINN)*

Octamilamina; Octamylaminum; Octisamyl hydrochloride (octamylamine hydrochloride); Октамиламин.

N-Isopentyl-1,5-dimethylhexylamine.

$C_{13}H_{29}N$=199.4

CAS — 502-59-0 (octamylamine); 5964-56-7 (octamylamine hydrochloride).

UNII — S0737084O9.

Profile

Octamylamine is a smooth muscle relaxant that has been used as an antispasmodic. The hydrochloride and mucate salts have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Octinum-D.

Octanoic Acid *(USAN, rINN)*

Acide caprylique; Acide Octanoïque; Ácido caprílico; Ácido octanoico; Ácido octílico; Ácido octoico; Acidum Caprylicum; Acidum Octanoicum; Caprylic Acid; Caprylsäure; Kaprilo rūgštis; Kaprilsav; Kaprylsyra; Kapryylihappo; Kwas kaprylowy; Kyselina oktanová; Octanoico, ácido; Octoic Acid; Octylic Acid; Октаноевая Кислота.

$CH_3.(CH_2)_6.CO_2H$=144.2

CAS — 124-07-2.

UNII — OBL58JN025.

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

Ph. Eur. 8: (Caprylic Acid; Octanoic Acid BP 2014). A clear, colourless or slightly yellowish, oily liquid. Very slightly soluble in water; very soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides.

USNF 31: (Caprylic Acid). A clear, colorless or slightly yellowish, oily liquid. Very slightly soluble in water; very soluble in alcohol and in acetone. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers.

Sodium Octanoate *(rINNM)*

Caprilato sódico; Natrii Caprylas; Natrii Octanoas; Natrio kaprilatas; Natriumcaprylat; Nátrium-kaprilát; Natriumkaprylaatti; Natriumkaprylat; Natrium-oktanoát; Octanoate de Sodium; Octanoato de sodio; Octanoato sódico; Sodium Caprylate; Sodium, caprylate de; Натрия Октаноат.

$C_8H_{15}NaO_2$=166.2

CAS — 1984-06-1.

UNII — 9XTM81VK2B.

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

Ph. Eur. 8: (Sodium Caprylate). A white or almost white, crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

USNF 31: (Sodium Caprylate). A white crystalline powder. Very soluble or freely soluble in water; sparingly soluble in alcohol; freely soluble in acetic acid; practically insoluble in acetone. A 10% solution in water has a pH of 8.0 to 10.5.

Profile

Octanoic acid and its salts have antifungal activity.

Sodium octanoate is used to stabilise albumin solution against the effects of heat. Octanoic acid labelled with carbon-13 has been used in a breath test to measure gastric emptying.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Caprilate†.

Olaquindox *(BAN, rINN)*

Bay-Va-9391; Olaquindoxum; Олахиндокс.

2-(2-Hydroxyethylcarbamoyl)-3-methylquinoxaline 1,4-dioxide.

$C_{12}H_{13}N_3O_4$=263.3

CAS — 23696-28-8.

ATC Vet — QJ01MQ01.

UNII — G3LAW9U88T.

Profile

Olaquindox is an antibacterial added to animal feedstuffs as a growth promotor. Photoallergic reactions in animal handlers have been reported on exposure to olaquindox.

Oleander

Adelfa; Baladre; Common Oleander; Espirradeira; Laurier Rose; Oleanderblätter; Oleandri Folium; Rose Bay; Олеандр.

ATC Herb — HC01AX5003 (Nerium oleander: *leaf*); *HC01AX5004* (Nerium oleander: *root*).

UNII — 7KV510R6H6 (Nerium oleander *leaf*); *WO4WVF1WVM* (Nerium oleander *extract*).

Uses and Administration

The dried leaves of the oleander shrub, *Nerium oleander* (Apocynaceae), contain cardiac glycosides, including oleandrin. They have been used in the treatment of heart disorders. The flowers and bark have been used similarly.

Homoeopathy

Oleander has been used in homoeopathic medicines under the following names: Nerium oleander; Oleand.

Adverse Effects and Treatment

Oleander contains cardiac glycosides (see above) and toxicity, similar to that seen with digoxin, may occur after ingestion of any part of the plant; fatalities have been reported. Yellow oleander (*Thevetia peruviana*) also contains cardiac glycosides and has similar toxicity to oleander. Digoxin-specific antibody fragments may be used in the management of severe poisoning.

Treatment of adverse effects. References to the treatment of oleander poisoning or yellow oleander poisoning.

1. Shumaik GM, *et al.* Oleander poisoning: treatment with digoxin-specific Fab antibody fragments. *Ann Emerg Med* 1988; 17: 732–5.
2. Safadi R, *et al.* Beneficial effect of digoxin-specific Fab antibody fragments in oleander intoxication. *Arch Intern Med* 1999; 159: 2121–5.
3. Eddleston M, *et al.* Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. *Lancet* 2000; 355: 967–72.
4. Fonseka MM, *et al.* Yellow oleander poisoning in Sri Lanka: outcome in a secondary care hospital. *Hum Exp Toxicol* 2002; 21: 293–5.
5. de Silva HA, *et al.* Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; 361: 1935–8.
6. Eddleston M, *et al.* Ox-Col Poisoning Study collaborators. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008; 371: 579–87.
7. Peiris-John RJ, Wickremasinghe AR. Efficacy of activated charcoal in yellow oleander poisoning. *Ceylon Med J* 2008; 53: 33–5.
8. Rajapakse S. Management of yellow oleander poisoning. *Clin Toxicol* 2009; 47: 206–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Miroton†; *Mex.*: Verisan Triplex.

Homoeopathic Preparations. *Chile*: Bioactiv P; *Fr.*: Boripharm No 23; Dermo-Drainol†; *Ger.*: Arrhythmie-Gastreu N; Crataegus Herzcomplex; Hypotonie-Gastreu R44; *Neth.*: Entero-Gastreu R4.

Olive

Oleae folium (olive leaf); Olivier, feuille d' (olive leaf); Маслина; Олива.

UNII — 6HD2W46UEG (green olive); 2M6QWV94OC (black olive).

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract.

Ph. Eur. 8: (Olive Leaf; Oleae Folium). The dried leaf of *Olea europaea*. It contains a minimum of 5.0% of oleuropein ($C_{25}H_{32}O_{13}$ = 540.5), calculated on the dried basis. Protect from light.

Profile

The fresh or dried leaf of the olive, *Olea europaea* (Oleaceae), is used in herbal medicine for its antihypertensive and diuretic actions.

Olive fruit is the source of olive oil, p. 2575.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Olivevital†; *Ger.*: Olivysat†.

Multi-ingredient Preparations. *Austral.*: Airborne Immunity; Bioage Peripheral†; Cats Claw-Echine; Cold & Flu Relief; Echinacea Royale; Olive Leaf Plus; *Canad.*: Optomega; *Fr.*: B.O.P.; Dida; Tavmet; Ultraselem; *Ger.*: Antihypertonicum S; *Switz.*:

Gouttes pour le coeur et les nerfs; *Ukr.*: Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Cardiopress; Immunicare.

Olive Oil

Aceite de oliva; Alyvuogių aliejus; Azeite; Huile d'Olive; Olej z oliwek; Oliviöljy; Olivae Oleum; Olivaolaj; Olive huile d'; Olivenöl; Olivolja; Olivový olej; Оливковое Масло; Прованское Масло.

ATC Herb. — HD02WB5006 (Olea europaea: oil).

UNII — 6UYK2W1W1E.

Pharmacopoeias. In *Jpn.* Also in *USNF.*

Eur. (see p. vii) includes monographs for virgin olive oil and refined olive oil.

Ph. Eur. 8: (Olive Oil, Virgin; Olivae Oleum Virginale). The fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea*. It is a clear, yellow or greenish-yellow, transparent liquid. When cooled it begins to become cloudy at 10 degrees and becomes a butter-like mass at 0 degrees. Practically insoluble in alcohol; miscible with petroleum spirit (50 degrees to 70 degrees). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Olive Oil, Refined; Olivae Oleum Raffinatum). The fatty oil obtained by refining of crude olive oil. A suitable antoxidant may be added. It is a clear, colourless, or greenish-yellow, transparent liquid. When cooled it begins to become cloudy at 10 degrees and becomes a butter-like mass at about 0 degrees. Practically insoluble in alcohol; miscible with petroleum spirit (50 degrees to 70 degrees). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light. Store under an inert gas if intended for use in the manufacture of parenteral dosage forms.

USNF 31: (Olive Oil). The fixed oil obtained from the ripe fruits of *Olea europaea* (Oleaceae). It may contain suitable antoxidants. It is a pale yellow, or light greenish-yellow, oily liquid, having a slight characteristic odour. Slightly soluble in alcohol; miscible with carbon disulfide, with chloroform, and with ether. Store in airtight containers at a temperature not exceeding 40 degrees.

Profile

When taken internally, olive oil is nutrient, demulcent, and mildly laxative. It may also be given rectally (100 to 500 mL warmed to about 32 degrees) to soften impacted faeces (see Constipation, p. 1804.3).

Externally, olive oil is emollient and soothing to inflamed surfaces, and is used to soften the skin and crusts in eczema (p. 1684.1) and psoriasis (p. 1688.1), and as a lubricant for massage. It is used to soften ear wax (p. 1836.3).

Olive oil is used in the preparation of liniments, ointments, plasters, and soaps; it is also used as a vehicle for oily suspensions for injection.

Epidemiological evidence points to the cardiovascular benefits of olive oil in the diet. Olive leaf (p. 2574.3) is used in herbal medicine.

References.

1. Waterman E, Lockwood B. Active components and clinical applications of olive oil. *Altern Med Rev* 2007; 12: 331–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Malaysia*: Olivenol livin' Begin†; Olivenol; *Singapore*: Olivenol Livin' Active; Olivenol Livin' Begin; *UK*: Arjun Ear Drops; *Ukr.*: Vaxol (Ваксол).

Multi-ingredient Preparations. *Arg.*: Clinoleic; *Austral.*: Clinoleic; SMOFlipid; *Austria*: Clinoleic; OliClinomel; PeriOlimel; SMOFlipid; ZentroOlimel; *Belg.*: Clinoleic; OliClinomel; Olimel; PeriOlimel; *Canad.*: Clinoleic; Olimel; PeriOlimel; Pure Gardens; *Chile*: OliClinomel; *Cz.*: Clinoleic; OliClinomel; Olimel; PeriOlimel; SMOFKabiven; SMOFlipid; *Denm.*: Clinoleic; Numeta GE; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; *Fin.*: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; *Fr.*: Clinoleic; Maghora†; Menolistica; OliClinomel; Olimel; Olivalax; PeriOlimel; Phytosolaire†; SMOFKabiven; SMOFlipid; *Ger.*: Clinoleic; Numeta GE; OliClinomel†; Olimel; SMOFKabiven; SMOFlipid; *Gr.*: Clinoleic; Multimel; OliClinomel; SMOFKabiven; SMOFlipid; *Hong Kong*: SMOFlipid; *Hung.*: OliClinomel; SMOFlipid; *India*: Efatop-PE; Elure; *Irl.*: Clinoleic†; Numeta GE; OliClinomel; SMOFKabiven; SMOFlipid; Triomel; *Israel*: Clinoleic; OliClinomel; SMOFKabiven; SMOFlipid; *Ital.*: Acumel; Ad$_3$; Clinoleic; OliClinomel; Pasta Di Hoffmann; SMOFlipid; *Malaysia*: Olivenol livin' Vigor†; Olivenol livin' Youthful†; *Neth.*: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; *Norw.*: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; *NZ*: Clinoleic; OliClinomel; Snorenz; *Pol.*: Clinoleic; SMOFKabiven; SMOFlipid; *Port.*: Clinoleic; OliClinomel; SMOFKabiven; SMOFlipid; *Rus.*: Oliclinomel (ОлиКлиномель); SMOFlipid (СМОФлипид); *Singapore*: Clinoleic; Dhaxtra; Hepasil DTX†; Olivenol Livin' Vigor; Olivenol Livin' Youthful; Snoreeze; *Spain*: Aceite Acalorico; Clinoleic; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; *Swed.*: Clinoleic; Numeta GE; OliClinomel; Olimel; SMOFKabiven; SMOFlipid; *Switz.*: Clinoleic; Numeta; OliClinomel†; Olimel; PeriOlimel; SmofKabiven; SMOFlipid; *Thai.*: Clinoleic; OliClinomel; SMOFlipid; *Turk.*: Clinoleic; SMOFlipid; Snoreless; *UK*: Clinoleic; OliClinomel; SMOFlipid; Snor-Away; *Ukr.*: SMOFlipid (СМОФлипид); *USA*: Clinolipid; Mimyx†.

Pharmacopoeial Preparations

BP 2014: Olive Oil Ear Drops.

Ololiuqui

CAS — 2889-26-1 (isoergine); 478-94-4 (ergine); 2390-99-0 (chanoclavine); 548-43-6 (elymoclavine); 602-85-7 (lysergol).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for 'morning glory' seeds:

Flying saucers; Glories; Heavenly blue; Pearly gates; Tlitlilzin; Yaxce'lil.

Profile

Ololiuqui consists of the seeds of *Rivea corymbosa* or *Ipomoea tricolor* (*I. violacea*) both convolvulaceous plants similar to the garden plant 'morning glory', *Ipomoea purpurea*. The brown seeds of *R. corymbosa* are known as 'badoh' and the black seeds of *I. tricolor* as 'badoh negro'.

Ololiuqui has hallucinogenic properties and is considered to be sacred by some Mexican Indians. Alkaloidal fractions contain at least 5 closely related individual components, namely D-isolysergic acid amide (isoergine), D-lysergic acid amide (ergine), chanoclavine, elymoclavine, and lysergol.

The name 'ololiuqui' has been erroneously applied to seeds of *Datura meteloides* (Solanaceae).

Omega-6 Fatty Acids

n-6 Fatty Acids; Omega 6 Acids; Omega 6 Fatty Acids.

UNII — 116Z6MZN1M.

Profile

Omega-6 fatty acids are long-chain polyunsaturated fatty acids similar to omega-3 fatty acids (p. 1460.1) but with the first double bond in the n-6 position. They include arachidonic acid (p. 2446.1), linoleic acid (p. 2509.2), and gamolenic acid (p. 2509.2). Mixtures of omega-6 fatty acids, for example from evening primrose oil (p. 2502.2), have been used in skin-care products and nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Exomega; *Chile*: Exomega; *Fr.*: Exomega; Nutrilarm; Omegacoeur; *India*: Eriz; *Indon.*: Curbexon; *Ital.*: Eutears; Skinproject; *Venez.*: Exomega.

Onion

Cebolla; Cipolla; Oignon; Zwiebel; Лук Репчатый.

ATC Herb — HC10AW5001 (Allium cepa: bulb).

UNII — 492225Q21H.

Profile

Onion is the bulb of *Allium cepa* (Liliaceae). It has been reported to reduce platelet aggregation, lower serum cholesterol, and to enhance fibrinolysis. It has been used in preparations for the treatment of urinary-tract disorders and in topical preparations for scars and contractures.

Homoeopathy

Onion has been used in homoeopathic medicines under the following names: Cepa; Allium cepa; All. cepa.

General references.

1. WHO. Bulbus Allii Cepae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/3.html (accessed 05/02/10)

Cardiovascular disease. A review of controlled studies purporting to show beneficial effects of garlic and/or onion on cardiovascular risk factors found those studies to have severe methodological failings.[1]

1. Kleijnen J, *et al.* Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol* 1989; 28: 535–44.

Stings. An onion bulb was used to treat the wound caused by a blue-spotted stingray (*Dasyatis kuhlii*).[1] Pain relief occurred within 30 minutes.

1. Whiting SD, Guinea ML. Treating stingray wounds with onions. *Med J Aust* 1998; 168: 584.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Mederma†; *Israel*: Mederma; *Malaysia*: Mederma; *Pol.*: Alcep; *Rus.*: Allilchep (Аллилчеп); *Singapore*: Mederma; *USA*: Mederma.

Multi-ingredient Preparations. *Arg.*: Contractubex; Integrum; *Austral.*: Garlic Allium Complex; Gartech†; *Austria*: Contractubex; *Braz.*: Contractubex; *China*: Contractubex (康瑞保); *Cz.*: Contractubex; *Fr.*: Amana Cellium; Androlistica; Pelvimag; *Ger.*: Contractubex; *Gr.*: Contractubex; *Hong Kong*: Contractubex; *Hung.*: Contractubex; *India*: Contractubex; Hexilak; *Indon.*: Mederma; *Ital.*: Skarflex; *Malaysia*: Palmer's Cocoa Butter Formula Scar Serum; *Mex.*: Contractubex; Mederma; *Philipp.*: Contractubex; Hiruscar; *Pol.*: Alcepalan†; Cepan; Cepasmel; Cepastil; Contractubex; *Rus.*: Contractubex (Контрактубекс); *Singapore*: Androlistica; Erase; Hiruscar; Scar Esthetique; *Switz.*: Contractubex; *Turk.*: Contractubex; *Ukr.*: Contractubex (Контрактубекс); Uronephron (Уронефрон).

Homoeopathic Preparations. *Austral.*: Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Hay Fever; Respatona Head Cold; *Austria*: Apozema Allium Cepa compositum; Cepa Med Complex; Famulan; Globuli gegen Heiserkeit; Globuli gegen Schnupfen Nr 1; Luffa Med Complex; *Canad.*: Allergies; Allergy Relief†; Cold Tablets with Zinc†; Coryzalia; EnurAid; Hay Complex†; Hay Fever; Hayfever; Homeo-Form AL†; Homeo-Form SI†; Homeodel 15†; Homeodel 21†; Hylamine HF; Hylands Formula CZ; Hylands Formula B; Kids Allergies; Pollen Plus; Sabalia; Sinus; *Chile*: Allium Compuesto; Rinoplex; *Cz.*: Coryzalia; Rhinallergy; *Fr.*: Allium Cepa Compose; Coryzalia; Dolistamine†; Polyrhinium; Rhinallergy; *Ger.*: Muco-cyl L Ho-Len-Complex; Schleimhaut-Komplex L Ho-Fu-Complex; Sinapis nigra N Oligoplex; *Hung.*: Coryzalia; *Neth.*: Cold Care; Coryzalia; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Mercurialis zalf; Nisyspray; Sniffle Care; *Port.*: Coryzalia; *Rus.*: Coryzalia (Коризалия); Famulan (Фамулан); *Switz.*: Alceprin-N; Coryzalia; Gouttes contre les rhumes des foins†; Nelsons Pollenna†; Polyrhinium; Rhinallergy; Spagyrhin; *UK*: Pollenna; *Ukr.*: Coryzalia (Коризалия); *USA*: Preferred Remedies Allergy; Preferred Remedies Sinus.

Ononis

Arrête-Boeuf; Bugrane, racine de; Busktõmerot; Dirvenių šaknys; Gatuňa; Hauhechelwurzel; Jehlicový kořen; Ononidis Radix; Piikkiorakonjuuri; Racine de Bugrane; Radix Ononidis; Restharrow Root; Spiny Restharrow; Tõvisesiglice-gyökér; Стальник Колючий (*Ononis spinosa*).

ATC Herb — HG048W5023 (Ononis spinosa: root).

UNII — RP849691SM (Ononis spinosa); FD2FMC53M1 (Ononis spinosa root).

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

Ph. Eur. 8: (Restharrow Root). The whole or cut, dried root of *Ononis spinosa*.

Profile

Ononis has diuretic activity. It has been used in herbal preparations for the treatment of oedema, urinary-tract disorders, rheumatic disorders, and constipation.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Nierentee St Severin; Uropurat†; *Canad.*: Entschlackungstee N†; *Cz.*: Species Urologicae Planta; Urologicka Cajova Smes; *Fr.*: Depuratum; Schoum; *Ger.*: Alasenn; Aqualibra; Biofax†; Hevert-Blasen-Nieren-Tee N†; Nephroselect M; Renob Blasen- und Nierentee†; *Ital.*: Slimmer Plus; Soluzione Schoum; *Pol.*: Betasol; Diuronis; *Rus.*: Herbion Urological Drops (Гербион Урологические Капли); *Switz.*: Demonatur Dragees pour les reins et la vessie†; Herbaprosta-Caps N†; Nephrosolid; *Ukr.*: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†.

Homoeopathic Preparations. *Canad.*: Male +; *Cz.*: Galium; *Fr.*: Berberis Complexe No 83; L 8; *Ger.*: Heweberberol; metasolidago S†; Pascodem.

Bitter Orange

Aurantii amari flos (bitter-orange flower); Aurantii Amari Pericarpium (bitter orange fruit); Bigaradier; Chéng Pí; Karčiavaisių citrinmedžių žiedai (bitter-orange flower); Keserű narancs virág (bitter-orange flower); Květ hořkého pomeranče (bitter-orange flower); Naranja Amarga; Naranja amarga, corteza de; Oranger amer, fleur d' (bitter-orange flower); Owocnia pomarańczy gorzkiej (bitter orange fruit); Pomeransblomma (bitter-orange flower); Pomeranssinkukka (bitter-orange flower); Pomeranze; Seville Orange; Померанец; Апельсин.

The symbol † denotes a preparation no longer actively marketed

ATC Herb — HN05CM5002 (Citrus aurantium: *flower*); *HA03AW5013* (Citrus aurantium: *peel*); *HA09WA5008* (Citrus aurantium: *peel*).
UNII — 055456JHI7 (Citrus aurantium *fruit rind*); *DQD16J2B5O* (Citrus aurantium *fruit*); *O730ZX2Z83* (Citrus aurantium *flower*).

Pharmacopoeias. *Eur.* includes the dried peel and flowers. *Jpn* includes the peel.

Ph. Eur. 8: (Bitter-orange Epicarp and Mesocarp; Aurantii amari epicarpium et mesocarpium; Dried Bitter-orange Peel BP 2014). The dried epicarp and mesocarp of the ripe fruit of *Citrus aurantium*, partly freed from the white spongy tissue of the mesocarp and endocarp, containing a minimum of 2.0% v/w of essential oil, calculated with reference to the anhydrous drug. It has an aromatic odour and a spicy bitter taste.

Ph. Eur. 8: (Bitter-orange Flower; Aurantii amari flos). The whole, dried, unopened flower of *C. aurantium* subsp. *aurantium* containing a minimum of 8.0% of total flavonoids, expressed as naringin ($C_{27}H_{32}O_{14}$ = 580.5), calculated with reference to the dried drug.

Profile

The dried peel of the bitter orange, *Citrus aurantium* subsp. *aurantium* (*Citrus aurantium* subsp. *amara*) (Rutaceae) is used as a flavour and for its bitter and carminative properties. Bitter-orange oil is an essential oil prepared from fresh bitter-orange peel that is similar to sweet orange oil (below). Both bitter-orange oil and petitgrain bigarade oil (prepared from the leaves and twigs) are used in aromatherapy.

The flowers are an ingredient of herbal remedies used for nervous and sleep disorders. Bitter-orange flower is the source of Neroli Oil (p. 2568.3).

The whole dried immature fruit is used similarly to the dried peel. In Chinese medicine, the dried immature fruits are known as zhi shi and zhi qiao. Extracts of bitter orange may have sympathomimetic properties (see below).

Photosensitivity is associated with citrus oils.

Action and use. *Citrus aurantium* was one of the most frequently used herbal remedies in Puerto Rico.[1] Indications included sleep disorders, gastrointestinal disorders, respiratory ailments, and raised blood pressure.

The volatile oil of dried bitter-orange peel has shown antifungal activity.[2]

Bitter-orange extract has been added to herbal weight loss remedies as it contains the sympathomimetic synephrine (a name that has been used for both phenylephrine and oxedrine), which is claimed to increase metabolism and promote thermogenesis, although efficacy is not proven. Variant angina[3] and ischaemic colitis[4] have been reported in patients taking dietary supplements containing bitter orange, and reports of serious cardiovascular adverse effects possibly associated with the synephrine content of bitter orange present in such preparations have been received in Canada.[5,6] Raised systolic and diastolic blood pressure and heart rate were seen after ingestion of a proprietary bitter orange preparation in one small randomised placebo-controlled crossover study.[7] However, in a similar study[8] comparing a single-ingredient bitter orange preparation with a combination preparation, adverse haemodynamic effects appeared to be related to the additional presence of other possible stimulants such as caffeine, rather than directly proportional to the dose of bitter orange alone.

1. Hernández L, *et al.* Use of medicinal plants by ambulatory patients in Puerto Rico. *Am J Hosp Pharm* 1984; 41: 2060–4.
2. Ramadan W, *et al.* Oil of bitter orange: new topical antifungal agent. *Int J Dermatol* 1996; 35: 448–9.
3. Gange CA, *et al.* Variant angina associated with bitter orange in a dietary supplement. *Mayo Clin Proc* 2006; 81: 545–8.
4. Sultan S, *et al.* Ischemic colitis associated with use of a bitter orange-containing dietary weight-loss supplement. *Mayo Clin Proc* 2006; 81: 1630–1.
5. Health Canada. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *Can Adverse React News* 2004; 14 (4): 3–4. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 06/08/08)
6. Health Canada. Bitter orange or synephrine: update on cardiovascular adverse reactions. *Can Adverse React News* 2007; 17 (2): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 06/08/08)
7. Bui LT, *et al.* Blood pressure and heart rate effects following a single dose of bitter orange. *Ann Pharmacother* 2006; 40: 53–7.
8. Haller CA, *et al.* Hemodynamic effects of ephedra-free weight-loss supplements in humans. *Am J Med* 2005; 118: 998–1003.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Calmtabs; *Austral.*: Kick-Start Detox; Metabolift Fat Burner; *Austria*: China-Eisenwein†; Eicebaer; Klosterfrau Melissengeist; Mariazeller; Montana; Pervivo; Sigman-Haustropfen; St Bonifatius-Tee†; Tussimont; *Braz.*: A Saude da Mulher; *Canad.*: Trim-Fit†; *Chile*: Propolkit; *Cz.*: Klosterfrau Melisana; *Fr.*: Biofirm; Boribel Tisane No 8†; Calmotisan†; Diatisan†; Elixir Bonjean†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Quintonine†; Santane N_5; Solaire; Vegetoserum†; *Ger.*: Amara-Pascoe; Carminativum-Hetterich; Gallexier; Klosterfrau Melissengeist; Montana N; Sedovent†; *Hung.*: Bittner; China; Klosterfrau Melisana; Montana; *Indon.*: Jesscool†; *Israel*: Passiflora; *Ital.*: Altadrine; Gastro-Pepsin; Idren; *Pol.*: Doppelherz Energovital Tonik†; Herbaton†; Krople Zoladkowe†; Krople Zoladkowe; Pervivo; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Melissa (Доппельгерц Мелисса); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *S.Afr.*: Versterkdruppels; *Singapore*: Bio-Taches†; Chitosano; *Spain*: Sedonat; *Switz.*: DemoPectol; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; *Turk.*: Nevrol Cemal; *UK*: Vital Eyes; *Ukr.*: Lipomin (Липомин); Liponorm (Липонорм).

Homoeopathic Preparations. *Fr.*: Poconeol no 58.

Pharmacopoeial Preparations
BP 2014: Concentrated Compound Gentian Infusion; Concentrated Orange Peel Infusion; Orange Peel Infusion; Orange Syrup;
Ph. Eur.: Bitter-Orange-Epicarp and Mesocarp Tincture.

Sweet Orange

Naranja; Апельсин Сладкий.
ATC Herb — HA09WA5009 (Citrus aurantium: *unripe fruit*).

Pharmacopoeias. *Swiss* includes the ripe fresh fruit of *Citrus sinensis*.

Chin. includes under the name Immature Orange Fruit (Fructus Aurantii Immaturus; Zhishi) both the dried immature fruit of *Citrus aurantium* and its cultivated varieties or the dried young fruit of *C. sinensis*.

Profile

Sweet orange, *Citrus sinensis* (*Citrus aurantium* var. *dulcis*) (Rutaceae), is an ingredient of herbal remedies used for nervous and sleep disorders. The peel is the source of sweet orange oil (below). Citrus fruits are a source of vitamin C (p. 2110.3).

Photosensitivity is associated with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: GR² Control Appetite Reducer; Vitamin C - Threshold Controlled; *Austria*: Magentee St Severin; Mariazeller; Pervivo; *Canad.*: Floradix Kindervital†; Salusan†; *Cz.*: Passedan†; *Fr.*: Calmiflorine†; Santane V_3†; *Hung.*: Bittner; *Pol.*: Pervivo; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *Switz.*: Femisan.

Pharmacopoeial Preparations
USNF 31: Orange Syrup; Sweet Orange Peel Tincture.

Sweet Orange Oil

Apelsininių citrinmedžių vaisių žievelių eterinis aliejus; Apelsinolja; Appelsiininkuoriöljy; Arancia Dolce Essenza; Aurantii Dulcis Aetheroleum; Aurantii Dulcis Pericarpii Etheroleum; Essence of Orange; Essence of Portugal; Essência de Laranja; Naranja, aceite esencial de; Orange douce, huile essentielle d'; Orange Oil; Silice oplodí sladkého pomeranče; Süssorangenschalenöl; Масло Сладкого Апельсина; Апельсиновое Масло, Сладкое.
ATC Herb — HN05CM5001 (Citrus aurantium: *essential oil*).
UNII — AKN3KSD11B.

NOTE. The oil from the flowers of *Citrus aurantium* var. *amara* is known as neroli oil or orange flower oil (p. 2568.3).

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

Ph. Eur. 8: (Sweet Orange Oil). An essential oil obtained without heating, by suitable mechanical treatment from the fresh peel of the fruit of *Citrus sinensis* (*Citrus aurantium* var. *dulcis*). A suitable antoxidant may be added. It contains 0.4 to 0.6% α-pinene, 0.02 to 0.3% β-pinene, 0.2 to 1.1% sabinene, 1.7 to 2.5% β-myrcene, 92.0 to 97.0% limonene, 0.1 to 0.4% octanal, 0.1 to 0.4% decanal, 0.2 to 0.7% linalol, 0.02 to 0.10% neral, 0.02 to 0.5% valencene, and 0.03 to 0.02% geranial.

A clear, pale yellow to orange, mobile liquid, which may become cloudy when chilled. It has a characteristic odour of fresh orange peel. Relative density 0.842 to 0.850. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Orange Oil). The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Rutaceae), containing not less than 1.2% w/v and not more than 2.5% w/v of aldehydes, calculated as decanal ($C_{10}H_{20}O$ = 156.3). It may be California-type or Florida-type orange oil. Store in well-filled airtight containers.

Profile

Sweet orange oil is used as a flavour, in perfumery, and in aromatherapy. It is used in the preparation of terpeneless orange oil. Photosensitivity reactions have been reported with citrus oils.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; *Canad.*: Melisana†; *Cz.*: Coldastop; Pleumolysin; *Fr.*: Aromadetox†; Aromazen†; Thermo Gomenol; *Ger.*: GeloSitin; *Hong Kong*: Magesto; *Hung.*: Perskindol Classic; *Malaysia*: Bio-Enhanced Fish Oil Plus; *Switz.*: Perskindol Classic; Perskindol Classic; Sibrovita†; *Turk.*: Myo-Oil; Nevrol Cemal.

Pharmacopoeial Preparations
USNF 31: Compound Orange Spirit.

Terpeneless Orange Oil

Naranja sin terpeno, aceite esencial de; Oleum Aurantii Deterpenatum; Апельсиновое Масло Бестерпеновое.

Pharmacopoeias. In *Br.*

BP 2014: (Terpeneless Orange Oil). A clear yellow or orange-yellow liquid, visibly free from water, with the odour and taste of orange, prepared by concentrating orange oil under reduced pressure until most of the terpenes have been removed, or by solvent partition. It contains not less than 18% w/w of aldehydes calculated as decanal ($C_{10}H_{20}O$ = 156.3). Soluble 1 in 1 of alcohol (90%). Store in well-filled containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Terpeneless orange oil consists chiefly of the free alcohols (+)-linalol and (+)-terpineol. It is used as a flavour. It is stronger in flavour and more readily soluble than the natural oil. Photosensitivity is associated with citrus oils.

Preparations

Pharmacopoeial Preparations
BP 2014: Compound Orange Spirit.

Orazamide *(rINN)*

AICA Orotate; Orazamida; Orazamidum; Oroxamide; Оразамид.
5-Aminoimidazole-4-carboxamide orotate dihydrate.
$C_5H_{10}N_5O_5.2H_2O$=318.2
CAS — 2574-78-9 (anhydrous orazamide); 60104-30-5 (orazamide dihydrate).
UNII — CLY9MRR8FV.

Profile

Orazamide has been given orally in the treatment of liver disorders.

Orchis Mascula

Early Purple Orchid; Ятрышник Мужской.
UNII — 4119KOT30J (Orchis mascula); *6H1JQK35LA* (Orchis mascula *flower*).

Profile

Orchis mascula, which is alleged to have aphrodisiac properties, has been used in herbal preparations for male sexual disorders.

Salep, a flour made from the dried ground tubers of *Orchis mascula* and various other species of orchid, contains a nutritious mucilage called bassorin; ice-cream made from salep is a great delicacy in Turkey.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Speman (Спеман); Speman Forte (Спеман Форте); Tentex (Тентекс); *Ukr.*: Confido (Конфидо)†; Speman (Спеман); Trypsidan (Трипсидан)†.

Oregano

Dost; Dostenkraut; Origan; Origani herba; Origani Vulgaris Herba; Wild Marjoram; Орегано.
CAS — 8007-11-2 (origanum oil).
UNII — 0E5AT8T16U (oregano); 38SNL0F81Z (Origanum vulgare *subsp. hirtum*); *39736Z7Q8W (origanum oil).*

NOTE. Distinguish from Marjoram, p. 2550.1.

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

Ph. Eur. 8: (Oregano). The dried leaves and flowers, separated from the stems, of *Origanum onites* or *O. vulgare* subsp. *hirtum*, or a mixture of both species. It contains a minimum of 2.5% v/w of essential oil, which contains a minimum of 60% of carvacrol and thymol, calculated with reference to the anhydrous drug. Protect from light.

Profile

The aerial parts of oregano, *Origanum onites* (Lamiaceae), or *O. vulgare* or its subspecies, are used as a culinary herb and in herbal preparations.

There is some confusion over the naming of origanum oils. Oil from *O. vulgare* has been used medicinally. Origanum Oil is the oil obtained from *Coridothymus capitatus* (*Thymus capitatus*) but oils from other related species may also be referred to as origanum oils, and Oil of Origanum was also given as a synonym for Thyme Oil in BPC 1949. Preparations listed in *Martindale* as containing origanum oil may contain an oil from any of these related species.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Asthmatee EF-EM-ES; Baby Luuf; ***Canad.***: Defense; Para-Gone; Relax Plus; ***Cz.***: Bronchosan†; Pytokliman Planta; ***Fr.***: Dida; Santane D_5†; ***Hung.***: Baby Luuf; ***Pol.***: Herbolen D†; Herbolen†; ***Rus.***: Bronchosan (Бронхосан); Pectorales Species No 1 (Грудной Сбор 1); Sedativae Species No 3 (Седативный Сбор 3); Urocholesan (Урохолесан); Valoserdin (Валосердин); ***Spain***: Pazbronquial; ***Switz.***: Demonatur Capsules contre les refroidissements; ***Ukr.***: Bronchosan (Бронхосан)†; Klimased (Климасед); Urolesan (Уролесан).

Homoeopathic Preparations. ***Fr.***: Poconeol no 9.

Oregon Grape

Barberry; Holly Barberry; Mahonia; Mountain Grape; Sowberry; Магония Падуболистная (*Mahonia aquifolium*).

ATC Herb — HN02BWS004 (Mahonia aquifolium: *bark*); *HD05AX5002* (Mahonia aquifolium: *bark*).

UNII — J4WG1JVR05 (Mahonia aquifolium); *P119S5ERN* (Mahonia aquifolium *fruiting top*); *746TB9VNDP* (Mahonia aquifolium *root*); *VZJ9F3C3SB* (Mahonia aquifolium *root bark*).

NOTE. The names Barberry, Oregon Grape, and Sowberry have been applied to both Oregon Grape and European Barberry (see p. 2502.1).

Profile

The rhizome and root of the Oregon grape, *Berberis aquifolium* (*Mahonia aquifolium*) (Berberidaceae) is used orally in herbal medicine mainly for gastrointestinal disorders and topically for skin disorders.

Berberis aquifolium is a source of berberine (p. 2455.1).

Homoeopathy

Oregon grape has been used in homoeopathic medicines under the following names: Berberis aquifolium; Berber aqui; Berb. aq.

References.

1. Gulliver WP, Donsky HJ. A report on three recent clinical trials using Mahonia aquifolium 10% topical cream and a review of the worldwide clinical experience with Mahonia aquifolium for the treatment of plaque psoriasis. *Am J Ther* 2005; 12: 398–406.
2. Bernstein S, *et al.* Treatment of mild to moderate psoriasis with Relieva, a Mahonia aquifolium extract—a double-blind, placebo-controlled study. *Am J Ther* 2006; 13: 121–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: DermaCo; ***Ukr.***: Hepahealth (Гепахелс).

Homoeopathic Preparations. ***Austral.***: Elimitona Slim & Detox; Elimitona; ***Austria***: Rubisan; Sensicare; ***Canad.***: Endoteel†; ***Cz.***: Rubisan; ***Fr.***: Euphorbium Complexe No 88; ***Ger.***: Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Derma-Plantin†; Ekzevowen; Hewelymphon N†; Rubisan; ***Hung.***: Rubisan; ***Neth.***: Rubisan†; ***Rus.***: Psoriaten (Псориатен); ***Switz.***: Omida Rubiderm; ***Ukr.***: Psoriaten (Псориатен).

Orlistat *(BAN, USAN, rINN)*

Orlipastat; Orlistaatti; Orlistatum; Ro-18-0647; Ro-18-0647/002; Tetrahydrolipstatin; Орлистат.

N-Formyl-L-leucine, ester with (3*S*,4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]-2-oxetanone; (*S*)-1-[(2*S*,3*S*)-3-Hexyl-4-oxo-oxetan-2-ylmethyl]dodecyl *N*-formyl-L-leucinate.

$C_{29}H_{53}NO_5$=495.7.

CAS — 96829-58-2.

ATC — A08AB01.

ATC Vet — QA08AB01.

UNII — 95M8R751W8.

Pharmacopoeias. In *US*.

USP 36: (Orlistat). A white to off-white fine powder or fine powder with lumps. Practically insoluble in water; very soluble in methyl alcohol and in alcohol; freely soluble in chloroform. Store at a temperature between 2 degrees and 8 degrees.

Uses and Administration

Orlistat is a gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat. It is used together with dietary modification in the management of obesity (p. 2315.1), i.e. in patients with a BMI of 30 kg/m² or greater. It may also be used in overweight patients with a BMI of 27 kg/m² or more if there are associated risk factors. Orlistat is given orally in a usual dose of 120 mg three times daily, immediately before, during, or up to 1 hour after meals. The patient's diet should be reduced in calories and nutritionally balanced with 30% of calories obtained from fat, and the daily intake of the major nutrients spread over the 3 main meals. If a meal is missed or contains no fat, the dose should be omitted. Orlistat therapy should be stopped if the patient does not lose at least 5% of their body-weight during the first 12 weeks of therapy. Orlistat may also be given in a lower dose of 60 mg three times daily in patients with a BMI of 28 kg/m² or more irrespective of any risk factors.

References.

1. Lucas KH, Kaplan-Machlis B. Orlistat—a novel weight loss therapy. *Ann Pharmacother* 2001; 35: 314–28.
2. Keating GM, Jarvis B. Orlistat: in the prevention and treatment of type 2 diabetes mellitus. *Drugs* 2001; 61: 2107–21.
3. Snider LJ, Malone M. Orlistat use in type 2 diabetes. *Ann Pharmacother* 2002; 36: 1210–18.
4. Henness S, Perry CM. Orlistat: a review of its use in the management of obesity. *Drugs* 2006; 66: 1625–56.
5. Filippatos TD, *et al.* Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Safety* 2008; 31: 53–65.
6. Anonymous. Over-the-counter weight loss with orlistat? *Drug Ther Bull* 2009; 47: 125–7.

Adverse Effects

Gastrointestinal disturbances, including faecal urgency and incontinence, flatulence, and fatty stools or discharge, are the most frequently reported adverse effects during treatment with orlistat, especially when taken with a high-fat diet. Other reported effects have included headache, anxiety, fatigue, rectal bleeding, and menstrual irregularities. Severe liver damage with hepatocellular necrosis or acute hepatic failure have been reported rarely in patients taking orlistat, and some of these cases have resulted in liver transplant and death. There have been concerns about an increased risk of breast cancer and colon cancer in patients taking orlistat but the FDA considers that there is no evidence of a causal link.

Effects on the cardiovascular system. A report of hypertension associated with orlistat therapy.[1] Blood pressure decreased on stopping orlistat and increased again on rechallenge. The authors noted that 13 cases of hypertension associated with orlistat had been reported to the manufacturers.

1. Persson M, *et al.* Orlistat associated with hypertension. *BMJ* 2000; 321: 87.

Effects on the skin. Lichenoid drug eruption affecting the vulva, feet, and axillae has been reported in a woman during orlistat treatment.[1] Symptoms resolved on stopping orlistat with only the vulval lesions requiring topical treatment with mometasone furoate 0.1%.

1. Sergeant A, *et al.* Lichenoid eruption associated with orlistat. *Br J Dermatol* 2006; 154: 1020–21.

Precautions

Orlistat should not be given to patients with chronic malabsorption syndrome or cholestasis and should be given with caution to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis. Adjustments to dosage of hypoglycaemics may be necessary in patients with type II diabetes because of improved metabolic control after weight loss in these patients. Patients reporting severe and/or persistent rectal bleeding with orlistat should undergo further investigation. Supplements of fat-soluble vitamins may be necessary during long-term therapy, but they should be taken at least 2 hours before or after an orlistat dose or at bedtime. Hormonal contraceptive failure may occur in the event of severe diarrhoea with orlistat, and patients are advised to use an additional contraceptive method.

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Interactions

Orlistat may reduce the absorption of fat-soluble vitamins. In patients taking warfarin, international normalised ratio should be monitored during treatment with orlistat. A reduction in ciclosporin concentrations to subtherapeutic levels has been reported in transplant recipients given orlistat (see p. 1953.2). Hypothyroidism has been described in a woman stabilised on levothyroxine sodium, within 2 weeks of starting orlistat (see p. 2342.1). Orlistat may decrease the absorption of antiepileptics and thereby increase the risk of seizures. Orlistat may also reduce the absorption of propafenone. For the possibility of hormonal contraceptive failure with orlistat see Precautions, above. Use of orlistat with acarbose should be avoided as the combination has not been studied.

Pharmacokinetics

Orlistat is minimally absorbed after oral doses. About 97% of a dose is excreted in the faeces, with 83% as unchanged orlistat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crisplus; Fingras; Frugal; Liposol; Oleofin; Xenical; Xeniplus†; Xinplex; ***Austral.***: Xenical; ***Austria***: Alli; Xenical; ***Belg.***: Alli; Xenical; ***Braz.***: Lipiblock; Xenical; ***Canad.***: Xenical; ***Chile***: Adell; Liberat; Oradiet; Sagras; Symfona; Viplena; Xenical; ***China***: Xenical (赛尼可); ***Cz.***: Alli; Xenical; ***Denm.***: Alli†; Xenical; ***Fin.***: Xenical; ***Fr.***: Alli; Xenical; ***Ger.***: Alli; Xenical; ***Gr.***: Alli; Xenical; ***Hong Kong***: Alli; Xenical; ***Hung.***: Alli; Xenical; ***India***: Cobese; Lipocut; Lipophage; Obelit; Obiless; Obitrol; Olisat; Orlica; Orlimac; Orlitroy; ***Indon.***: Xenical; ***Irl.***: Alli; Xenical; ***Israel***: Alli; Xenical; ***Ital.***: Xenical; ***Malaysia***: Cuvarlix; Xenical; ***Mex.***: Amsafast; Leben-Celtics; Lindeza; Lysthin; Redustat; Vasdecom; Ventu; Xenical; ***Neth.***: Alli; Xenical; ***Norw.***: Alli†; Xenical; ***NZ***: Xenical; ***Philipp.***: Lesofat; Obestal; Xenical; ***Pol.***: Alli; Xenical; ***Port.***: Alli; Xenical; ***Rus.***: Alli (Алли); Orsoten (Орсотен); Xenical (Ксеникал); ***S.Afr.***: Xenical; ***Singapore***: Xenical; ***Spain***: Alli; Xenical; ***Swed.***: Alli; Xenical; ***Switz.***: Alli; Calobalin; Xenical; ***Thai.***: Xenical; ***Turk.***: Thincal; Xenical; ***UK***: Alli; Xenical; ***Ukr.***: Xenical (Ксеникал); ***USA***: Alli; Xenical; ***Venez.***: Xenical.

Pharmacopoeial Preparations

USP 36: Orlistat Capsules.

Ornipressin *(rINN)*

Ornipresina; Ornipressine; Ornipressinum; Орнипрессин.

[8-Ornithine]-vasopressin.

$C_{45}H_{63}N_{13}O_{12}S_2$=1042.2

CAS — 3397-23-7.

ATC — H01BA05.

ATC Vet — QH01BA05.

UNII — 1KTH6N080W.

Profile

Ornipressin is a synthetic derivative of vasopressin (p. 2642.3) with similar actions. It is reported to be a strong vasoconstrictor with only weak antidiuretic properties and is used to reduce bleeding during surgery. A solution containing up to 5 units in 20 to 60 mL of sodium chloride 0.9% is infiltrated into the area involved. Ornipressin has also been given by intravenous infusion for the treatment of bleeding oesophageal varices (under Monoethanolamine, p. 2563.1).

References.

1. Kam PC, Tay TM. The pharmacology of ornipressin (POR-8): a local vasoconstrictor used in surgery. *Eur J Anaesthesiol* 1998; 15: 133–9.
2. De Kock M, *et al.* Ornipressin (Por 8): an efficient alternative to counteract hypotension during combined general/epidural anesthesia. *Anesth Analg* 2000; 90: 1301–7.

Adverse effects. Acute pulmonary oedema occurred in a patient after infiltration of ornipressin (12 units in 40 mL isotonic saline) as a local vasoconstrictor during surgery.[1] It was suggested that no more than 100 milliunits/kg should be given in this manner.

1. Borgeat A, *et al.* Acute pulmonary oedema following administration of ornithine-8-vasopressin. *Br J Anaesth* 1990; 65: 548–51.

Hepatorenal syndrome. Ornipressin has been found to be of benefit[1-4] in the hepatorenal syndrome, a form of renal insufficiency associated with cirrhosis of the liver, and thought to be due to severe renal vasoconstriction secondary to systemic arterial vasodilatation. However, caution

in its use has been urged[2] because of the risk of ischaemic complications.

1. Lenz K, *et al.* Ornipressin in the treatment of functional renal failure in decompensated liver cirrhosis: effects on renal hemodynamics and atrial natriuretic factor. *Gastroenterology* 1991; 101: 1060–7.
2. Guevara M, *et al.* Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998; 27: 35–41.
3. Gülberg V, *et al.* Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology* 1999; 30: 870–5.
4. Restuccia T, *et al.* Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome: a case-control study. *J Hepatol* 2004; 40: 140–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: POR 8; *NZ*: POR 8; *S. Afr.*: POR 8.

Orotic Acid *(BAN, pINN)*

Acide Orotique; Ácido orótico; Acidum Oroticum; Animal Galactose Factor; Oroottihappo; Orótico, ácido; Orotsyra; Uracil-6-carboxylic Acid; Vitamin B_{13}; Vitamina B_{13}; Whey Factor; Оротовая Кислота.

1,2,3,6-Tetrahydro-2,6-dioxopyrimidine-4-carboxylic acid.

$C_5H_4N_2O_4$=156.1

CAS — 65-86-1 (anhydrous orotic acid); 50887-69-9 (orotic acid monohydrate).

UNII — 61H4T033ES (orotic acid); 91532S02AO (orotic acid monohydrate).

Profile

Orotic acid, an intermediate in the biosynthesis of pyrimidine nucleotides, occurs naturally in the body and is also found in milk. Orotic acid and its calcium, carnitine, choline, lithium, lysine, and potassium salts have been used in liver disorders. Some of these salts, as well as chromium, cyproheptadine, deanol (p. 2319.1), magnesium, and zinc orotates have been given as tonics or dietary supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Orotate.

Multi-ingredient Preparations. *Arg.*: Bil 13; Zimerol; *Austral.*: Potasi; *Hong Kong*: Hepatofalk†; Lipochol; *Mex.*: Lipovitasi-Or; *Philipp.*: Godex†; Godex; Inlex; Mitocore; Mitodex; Mitonerb; Mivex; Vita SL; *Rus.*: Vitamax (Витамакс)†; *S.Afr.*: Hepabionta†; *Spain*: Hepadif; Pleon†; *Thai.*: Lipochol; *UK*: Sugar Bloc; *Ukr.*: Energin (Энергин); Hepadif (Гепадиф); Hepadif (Гепадиф).

Homoeopathic Preparations. *Ger.*: Hepar comp.

Orthodichlorobenzene

Ortodiclorobenceno; Орто-дихлорбензол.

1,2-Dichlorobenzene.

$C_6H_4Cl_2$=147.0

CAS — 95-50-1.

UNII — 6PJ93I88XL.

Profile

Orthodichlorobenzene has been used as an ingredient of solutions for dissolving ear wax. It has also been used as a wood and furniture preservative. Orthodichlorobenzene is an irritant volatile liquid; lens opacities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Cerumol; *Switz.*: Cerumenol.

Oryzanol

Gamma orizanol; Gamma Oryzanol; Orizanol; γ-Oryzanol; γ-OZ; Гамма-оризанол.

Triacontanyl 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate.

$C_{40}H_{58}O_4$=603.0

CAS — 11042-64-1.

UNII — 5ST9XCL51M.

Profile

Oryzanol is a substance extracted from rice brain oil and rice embryo bud oil. It has been given orally in the treatment of hyperlipidaemias. It has also been used for its supposed effects on autonomic and endocrine function.

References.

1. Cicero AF, Gaddi A. Rice bran oil and gamma-oryzanol in the treatment of hyperlipoproteinaemias and other conditions. *Phytother Res* 2001; 15: 277–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Luo Bei Jing (络倍静); *Jpn*: Hi-Z.

Multi-ingredient Preparations. *Ital.*: Anasterol; Lenirose; *Jpn*: Q & P; Sin Q & P Gold†; *Singapore*: Gin-Vita.

Otilonium Bromide *(BAN, rINN)*

Bromuro de otilonio; Octylonium Bromide; Otilonii Bromidum; Otilonio, bromuro de; Otilonium, Bromure d'; SP-63; Отилония бромид.

Diethylmethyl[2-[4-(2-octyloxybenzamido)benzoyloxy]ethyl] ammonium bromide.

$C_{29}H_{43}BrN_2O_4$=563.6

CAS — 26095-59-0.

ATC — A03AB06.

ATC Vet — QA03AB06.

UNII — 21HN3N72PV.

Profile

Otilonium bromide is used in the symptomatic treatment of gastrointestinal disorders associated with smooth muscle spasms in oral doses up to 120 mg daily. It has also been given rectally and by nebuliser.

References.

1. Battaglia G, *et al.* Otilonium bromide in irritable bowel syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol Ther* 1998; 12: 1003–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bromotil; Motid; Pasminox; Spasmoctyl; *Belg.*: Spasmomen; *Braz.*: Lonium; *China*: Spasmomen (斯巴敏); *Cz.*: Spasmomen; *Gr.*: Doralin; Otilax; *Hong Kong*: Spasmomen; *Hung.*: Spasmomen; *India*: Menoctyl; *Indon.*: Spasmomen; *Israel*: Spasmomen; *Ital.*: Spasen; Spasmomen; *Mex.*: Debromu; Omuro; *Port.*: Spasmomen; *Spain*: Spasmoctyl; *Turk.*: Ekspaz; Spasmomen; *Ukr.*: Spasmomen (Спазмомен).

Multi-ingredient Preparations. *Arg.*: Pasminox Somatico; Spasmoctyl Somatico; *Ital.*: Spasen Somatico; Spasmomen Somatico.

Oxaceprol *(rINN)*

Acetylhydroxyproline; C061; Oxacéprol; Oxaceprolum; Оксацепрол.

(-)-1-Acetyl-4-hydroxy-L-proline.

$C_7H_{11}NO_4$=173.2

CAS — 33996-33-7.

ATC — D11AX09; M01AX24.

ATC Vet — QD11AX09; QM01AX24.

UNII — Q0XV76B96L.

Profile

Oxaceprol is reported to affect connective tissue metabolism and has been used in dermatology, to promote wound healing, and in rheumatic disorders. Adverse effects have included gastric pain, nausea, diarrhoea, dizziness, headache, and rashes.

References.

1. Bauer HW, *et al.* Oxaceprol is as effective as diclofenac in the therapy of osteoarthritis of the knee and hip. *Clin Rheumatol* 1999; 18: 4–9.
2. Herrmann G, *et al.* Oxaceprol is a well-tolerated therapy for osteoarthritis with efficacy equivalent to diclofenac. *Clin Rheumatol* 2000; 19: 99–104.
3. Krüger K, *et al.* Oxaceprol—a randomised, placebo-controlled clinical study in osteoarthritis with a non-conventional non-steroidal anti-inflammatory drug. *Clin Exp Rheumatol* 2007; 25: 29–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Joint; *Fr.*: Flammaspray; Jonctum Cica; *Ger.*: AHP 200; *Spain*: Tejuntivo†.

Multi-ingredient Preparations. *Spain*: Robervital†.

Oxalic Acid

Kwas szczawiowy; Oxálico, ácido.

$HO_2CCO_2H.2H_2O$=126.1

CAS — 144-62-7 (anhydrous oxalic acid); 6153-56-6 (oxalic acid dihydrate).

ATC Vet — QP53AG03.

UNII — 9E7R5L6H31 (oxalic acid); 0K2L2U59O (oxalic acid dihydrate).

Uses

Oxalic acid has varied industrial uses and has been used in escharotic preparations. Oxalic acid salts have been given orally and the urinary excretion of oxalate used as a screening test for lipid malabsorption.

Diagnostic use. References.

1. Rampton DS, *et al.* Screening for steatorrhoea with an oxalate loading test. *BMJ* 1984; 288: 1419. Correction. *Ibid.*: 1728.
2. Sangalenti O, *et al.* Urinary oxalate recovery after oral oxalic acid load: an alternative method to the quantitative determination of stool fat for the diagnosis of lipid malabsorption. *J Int Med Res* 1989; 17: 526–31.

Adverse Effects

On ingestion, severe gastroenteritis is produced by the corrosive action of oxalic acid and its soluble salts on the gastrointestinal tract. Burning of the mouth, throat, and oesophagus with ulceration may also occur. Hypoxia may occur in the presence of laryngeal oedema, and shock and hypotension may arise in severe cases. Oxalates can chelate body calcium following systemic absorption, and may produce symptoms of hypocalcaemia such as tetany, convulsions, and, in some cases, ventricular fibrillation. Oxalate crystals may be deposited in the blood vessels, brain, heart, liver, and lungs; deposition in the renal tubules leads to acute renal failure. The mean fatal dose of oxalates has been reported to be about 15 to 30 g, although death has occurred with much lower doses. Death may occur within a few hours of ingestion.

Fatalities have resulted from intravenous administration of sodium oxalate[1] or ingestion of oxalic acid.[2]

Crystals of calcium oxalate present in the sap of daffodils[3] or *Agave tequilana* plants[4] have been reported to contribute to the rash experienced by workers coming into contact with these plants.

1. Dvořáčková I. Tödliche Vergiftung nach intravenöser Verabreichung von Natriumoxalat. *Arch Toxikol* 1966; 22: 63–7.
2. Farré M, *et al.* Fatal oxalic acid poisoning from sorrel soup. *Lancet* 1989; ii: 1524.
3. Julian CG, Bowers FW. The nature and distribution of daffodil pickers' rash. *Contact Dermatitis* 1997; 37: 259–62.
4. Salinas ML, *et al.* Irritant contact dermatitis caused by needle-like calcium oxalate crystals, raphides, in Agave tequilana among workers in tequila distilleries and agave plantations. *Contact Dermatitis* 2001; 44: 94–6.

Treatment of Adverse Effects

After ingestion of oxalic acid, a dilute solution of any soluble calcium salt should be given to precipitate the oxalate; alternatively milk may be given. Oral activated charcoal has also been suggested if ingestion has occurred within 1 hour. Gastric lavage is contra-indicated by some centres given the corrosive nature of oxalic acid. Calcium gluconate 10% should be given intravenously to prevent tetany. Acute renal failure should be anticipated in surviving patients and calls for careful fluid management. Haemodialysis or peritoneal dialysis have also been suggested for the removal of oxalate in primary oxalosis in an attempt to prevent acute renal failure and correct hypocalcaemia.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: Solcoderm (恩可得); *Ger.*: Solco-Derman; *Hong Kong*: Solcoderm†; *Pol.*: Solcogyn; *Rus.*: Solcoderm (Солкодерм); Solcovagin (Солковагин); *Switz.*: Solcoderm; Solcogyn; *Ukr.*: Solcoderm (Солкодерм); Solcovagin (Солковагин).

Homoeopathic Preparations. *Fr.*: Berberis Complexe No 83; *Ger.*: Agnus castus comp†; *Switz.*: Regenaplex Nr 28a.

Oxalacetic Acid

Acid oxalacetic; Acid Oxalilacetic; Acide Oxaloacétique; Ácido Ossalacetico; Ácido Oxaloacético; Ketosuccinic Acid; Kwas Szczawiooctowy; Kyselina Oxaloctová; Oksaloetikkahappo; Oxaalazijnzuur; Oxälättiksyra; Oxalecetsav; Oxalessigsäure; Oxaloacetic Acid; Oxosuccinic Acid; Skåbenetiksåbe; Щавелевоуксусная Кислота.

2-Oxobutanedioic Acid.

$C_4H_4O_5$=132.1

CAS — 328-42-7 (oxalacetic acid); 108-56-5 (diethyl oxalacetate); 40876-98-0 (diethyloxalacetate sodium).

UNII — 2F39MM81J.

Profile

Oxalacetic acid is an intermediate in the citric acid cycle and therefore has an important role in cellular respiration. It has been used in a stabilised form as a nutritional supplement.

Homoeopathy

Salts and esters of oxaloacetic acid have been used in homoeopathic medicines but the precise identity is not always clear. The following names have been used: Sodium diethyloxalacetate; Diethyloxalacetate de sodium; Natrium oxalaceticum; Natriumoxalacetat.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Zeel; Zeel.

Homoeopathic Preparations. *Cz.*: Zeel Salbe†; *Ger.*: Hepar comp; Mucosa compositum; Zitronensaurezyklns-Heel; *Hung.*: Zeel; *Rus.*: Zeel T (Цель Т).

Oxogluric Acid

Acide alpha-cétoglutarique; Acide Oxoglurique; Acide 2-oxoglutarique; Ácido alfacetoglutárico; Acido 2-chetoglutarico; Acido 2-ossoglutarico; Acidum alpha-ketoglutaricum; Alfa-ketoglutársav; Alfa-ketoglutarsyra; Alfa-ketoglutarsyre; α-Ketoglutaric Acid; α-Ketoglutarsäure; Kwas alfa-ketoglutarowy; 2-Oxoglutaric Acid; α-Oxoglutaric Acid; 2-Oxoglutarová kyselina; 2-Oxoglutarsäure; 2-Oxopentandisäure; α-Кетоглутаратная кислота.

2-Oxopentanedioic Acid.

$C_5H_6O_5$=146.1

CAS — 328-50-7.

UNII — 8ID597Z82X.

Profile

Oxogluric acid is an intermediate in the citric acid cycle. It has been used as a dietary supplement and has also been used in preparations for vaginal disorders. The calcium and magnesium salts have also been used.

Homoeopathy

Oxogluric acid has been used in homoeopathic medicines under the following names: Acidum alpha ketoglutaricum; Ketoglutaricum acidum; Ketoglutaric acid; 2-Oxoglutarsäure.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Cetoglutaran†.

Multi-ingredient Preparations. *Ital.*: Gynegella P; Ipoazotal Complex.

Homoeopathic Preparations. *Ger.*: Hepar comp; Zitronensaurezyklus-Heel.

Ozagrel *(rINN)*

OKY-046 (ozagrel hydrochloride); Ozagrelum; Озагрел.

(*E*)-*p*-(Imidazol-1-ylmethyl)cinnamic acid.

$C_{13}H_{12}N_2O_2$=228.3

CAS — 82571-53-7.

UNII — L256JB984D.

Profile

Ozagrel is a thromboxane synthetase inhibitor that has been given orally as the hydrochloride for the treatment of asthma in doses of 200 mg twice daily. It has also been given as the sodium salt by intravenous infusion for the treatment of cerebrovascular disorders in a dose of 80 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Xin Kang (奥辛康); Ci He Ying (赐禾盈); Dan Lun (丹仑); Eryechang (二叶畅); Hong Bang (鸿邦); Hua Yi Mai (华益迈); Kang En (康恩); Kawin Di Ning (凯因迪宁); Qi Ming Lei Ao (齐铭雷奥); Qing Er (晴尔); Tai Ya Pu Xi (泰亚普昔); Zhou Bang (洲邦); *Jpn*: Cataclot; Domenan; Vega; Xanbon.

Palifermin *(BAN, USAN, rINN)* ⊗

AMJ-9701; Palifermina; Palifermine; Paliferminum; rHu-KGF; Палифермин.

24-163 Fibroblast growth factor 7 (human).

CAS — 162394-19-6; 178254-26-7.

ATC — V03AF08.

ATC Vet — QV03AF08.

UNII — QMS40680K6.

Uses and Administration

Palifermin is a human recombinant keratinocyte growth factor (KGF) used to reduce the incidence and duration of severe oral mucositis (see below) in patients with haematological neoplasms who receive myelotoxic chemotherapy with radiotherapy, followed by haematopoietic stem cell transplantation. The recommended course of palifermin is 6 doses of 60 micrograms/kg, by intravenous bolus injection. A dose is given on each of 3 consecutive days before, and 3 consecutive days after, myelotoxic therapy. Palifermin should not be given during, or for 24 hours before or after, myelotoxic therapy. Thus, the third pre-chemotherapy dose of palifermin should be given 24 to 48 hours before myelotoxic therapy, and the first post-chemotherapy dose of palifermin should be given after, but on the same day as, the haematopoietic stem cell infusion, and at least 4 days after the third pre-myelotoxic dose.

Mucositis. Palifermin is a human recombinant keratinocyte growth factor (KGF) that binds to KGF receptors and repairs damaged epithelium by stimulating the proliferation, differentiation, and migration of epithelial cells.[1,2] Controlled studies have shown it to be effective in reducing the severity and duration of oral mucositis (p. 732.1) in patients receiving myelotoxic therapy for haematological neoplasms and requiring haematopoietic stem cell support.[3,4] It has also shown benefit compared with placebo in reducing the incidence of oral mucositis and diarrhoea in patients receiving fluorouracil and leucovorin for metastatic colorectal cancer.[5]

1. Siddiqui MAA, Wellington K. Palifermin: in myelotoxic therapy-induced oral mucositis. *Drugs* 2005; 65: 2139–46.
2. McDonnell AM, Lenz KL. Palifermin: role in the prevention of chemotherapy- and radiation-induced mucositis. *Ann Pharmacother* 2007; 41: 86–94.
3. Spielberger R, *et al.* Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; 351: 2590–8.
4. Stiff PJ, *et al.* Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *J Clin Oncol* 2006; 24: 5186–93.
5. Rosen LS, *et al.* Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *J Clin Oncol* 2006; 24: 5194–5200.

Adverse Effects

Adverse reactions reported with palifermin therapy have included rash, erythema, oedema, pruritus, fever, perioral dysaesthesia, tongue discoloration and thickening, and altered taste. Skin hyperpigmentation and gastrointestinal and respiratory disturbances have also been reported. The safety and efficacy of palifermin in patients given treatment for non-haematological neoplasms has not been established; stimulation and growth of tumour cell lines have been found in *animal* and *in-vitro* models of non-haematopoietic human tumours.

Effects on the skin. Flexural hyperpigmentation has been reported in 5 white-skinned patients being treated with palifermin.[1] The lesions were described as ill-defined symmetrical hyperpigmented papillomatous plaques with slight erythema in the skin folds, especially affecting axillary and inguinal areas.

A papular eruption clinically resembling lichen planus or plane warts, with histologic features of verruca plana, and intertriginous erythema has been reported in a patient; the lesions resolved spontaneously without treatment.[2]

1. Sibelt LAG, *et al.* Palifermin-induced flexural hyperpigmentation: a clinical and histological study of five cases. *Br J Dermatol* 2008; 159: 1200–3.
2. King B, *et al.* Palifermin-associated papular eruption. *Arch Dermatol* 2009; 145: 179–82.

Interactions

In-vitro and *in-vivo* data suggest that palifermin binds to unfractionated as well as low-molecular-weight heparins, and licensed product information therefore recommends that such combinations should be used with care, although the clinical relevance is unclear.

Pharmacokinetics

The pharmacokinetics of palifermin were approximately dose-linear after a single intravenous dose in healthy subjects given larger than usual doses. The terminal elimination half-life is about 4.5 hours.

References.

1. Zia-Amirhosseini P, *et al.* Pharmacokinetics, pharmacodynamics, and safety assessment of palifermin (rHuKGF) in healthy volunteers. *Clin Pharmacol Ther* 2006; 79: 558–69.
2. Gillespie B, *et al.* Effect of renal function on the pharmacokinetics of palifermin. *J Clin Pharmacol* 2006; 46: 1460–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Kepivance; *Austria*: Kepivance; *Belg.*: Kepivance; *Canad.*: Kepivance; *Cz.*: Kepivance; *Denm.*: Kepivance; *Fin.*: Kepivance; *Fr.*: Kepivance; *Ger.*: Kepivance; *Gr.*: Kepivance; *Hung.*: Kepivance; *Irl.*: Kepivance; *Israel*: Kepivance; *Ital.*: Kepivance; *Neth.*: Kepivance; *Norw.*: Kepivance; *Pol.*: Kepivance; *Port.*: Kepivance; *Spain*: Kepivance; *Swed.*: Kepivance; *Switz.*: Kepivance; *UK*: Kepivance; *USA*: Kepivance.

Palladium

Paladij; Paladio; Paládio; Paladis; Paladiu; Paladium; Paladyum; Pallaadium; Pallad; Pallādijs; Palladín; Palladio; Pallădium; Палладий; Паладий.

Pd=106.42

CAS — 7440-05-3.

UNII — 5TWQ1V240M.

Profile

Palladium is a precious metal with similar properties and uses to platinum (p. 2593.1).

Homoeopathy

Palladium has been used in homoeopathic medicines under the following names: Palladium; Palladium metallicum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Passiflora Complex†; *Fr.*: Passiflora Compose.

Palmarosa Oil

Essência de Palma-rosa; Indian Geranium Oil; Turkish Geranium Oil.

CAS — 8014-19-5.

UNII — 0J3G3O53ST.

Profile

Palmarosa oil is derived from palmarosa (*Cymbopogon martini*, Poaceae) and is used in perfumery and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Singapore*: Teenstick; *UK*: Teenstick.

Palmidrol *(rINN)*

Palmidrolum; Пальмидрол.

N-(2-Hydroxyethyl)palmitamide.

$C_{18}H_{37}NO_2$=299.5

CAS — 544-31-0.

UNII — 6R8T1UDM3V.

Profile

Palmidrol is a naturally occurring lipid compound that may be isolated from soybean lecithin, egg-yolk, or peanut meal. It has been used as an immunostimulant. It is given orally in doses of 1 g two or three times daily for the treatment of respiratory-tract infections.

Pancreatic Enzymes

Панкреатические Ферменты.

Pancreatin *(BAN)* ⊗

Haimajauhe (pancreas powder); Kasos milteliai (pancreas powder); Pancréas, poudre de (pancreas powder); Pancreatina; Pancreatinum; Pancreatis pulvis (pancreas powder); Pankreaspulver (pancreas powder); Pankreatiini; Pankreatin; Pankreáz-por (pancreas powder); Панкреатин.

CAS — 8049-47-6.

UNII — FQ3DRG0N5K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US* as pancreatin or another pancreatic exocrine extract or both.

Ph. Eur. 8: (Pancreas Powder; Pancreatis Pulvis; Pancreatic Extract BP 2014). It is prepared from the fresh or frozen pancreases of mammals. It contains various enzymes having proteolytic, lipolytic, and amylolytic activities. Each mg of pancreas powder contains not less than 1 Ph. Eur. unit of total proteolytic activity, not less than 15 Ph. Eur. units of lipolytic activity, and not less than 12 Ph. Eur. units of amylolytic activity. A slightly brown, amorphous powder. Partly soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP 2014: (Pancreatin). A preparation of mammalian pancreas containing enzymes having protease, lipase, and amylase activity. Each mg of pancreatin contains not less than 1.4 FIP units of free protease activity, not less than 20 FIP units of lipase activity, and not less than 24 FIP units of

amylase activity. It may contain sodium chloride. A white or buff amorphous powder, free from unpleasant odour. Soluble or partly soluble in water forming a slightly turbid solution; practically insoluble in alcohol and in ether. Store at a temperature not exceeding 15 degrees.

USP 36: (Pancreatin). A substance containing enzymes, mainly amylase, lipase, and protease, obtained from the pancreas of the hog or of the ox. It is a cream-coloured, amorphous powder, having a faint, characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancreatin contains, in each mg, not less than 25 USP units of amylase activity, not less than 2 USP units of lipase activity, and not less than 25 USP units of protease activity. Pancreatin of a higher digestive power may be labelled as a whole-number multiple of the 3 minimum activities, or may be diluted with lactose, or with sucrose containing not more than 3.25% of starch, or with pancreatin of lower digestive power. Store in airtight containers at a temperature not exceeding 30 degrees.

Pancrelipase *(USAN)* ⊗

Pancrelipasa; Панкрелипаза.

CAS — 53608-75-6.

UNII — YOJ58O116E (pancrelipase amylase); 8MYC33932O (pancrelipase lipase); 3560D81V50 (pancrelipase protease).

Pharmacopoeias. In *US*.

USP 36: (Pancrelipase). A substance containing enzymes, mainly lipase, with amylase and protease, obtained from the pancreas of the hog. It is a cream-coloured, amorphous powder having a faint characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action. Pancrelipase contains, in each mg, not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity. Store in airtight containers preferably at a temperature not exceeding 25 degrees.

Units

The Ph. Eur. and USP units of protease activity depend upon the rate of hydrolysis of casein, those of lipase activity depend upon the rate of hydrolysis of olive oil, and those of amylase activity depend upon the rate of hydrolysis of starch. Because of differences in the assay conditions, the Ph. Eur. and USP units are not readily comparable.

FIP units of protease, lipase, and amylase activity are approximately equivalent to Ph. Eur. units.

Uses and Administration

Pancreatic enzymes (as pancreatin or pancrelipase) hydrolyse fats to glycerol and fatty acids, break down protein into peptides, proteoses and derived substances, and convert starch into dextrins and sugars. They are given orally in conditions of pancreatic exocrine deficiency such as pancreatitis and cystic fibrosis. They are available in the form of powder, capsules containing powder or enteric-coated granules (which may be opened before use and the contents sprinkled on soft food), enteric-coated tablets, or granules. If pancreatic enzymes are mixed with liquids or food the resulting mixture should not be allowed to stand for more than 1 hour before use. Histamine H_2-receptor antagonists, such as cimetidine or ranitidine, have been given an hour before a dose in an attempt to lessen destruction of the pancreatic enzymes by gastric acid, or proton pump inhibitors such as omeprazole may be used; alternatively, antacids may be given with the dose.

The dose of pancreatic enzymes is adjusted according to the needs of the individual patient and will also depend on the dosage form. In the UK, proprietary preparations generally provide about 5000 to 10000 units of lipase activity per dose-unit and usual doses, given with each meal, range from about 5000 to 56000 units of lipase activity (with varying proportions of protease and amylase activity, depending on the preparation). In the USA, doses providing up to 40000 USP units of lipase activity may be given with each meal. So-called high-strength or high-potency preparations are available for those receiving high doses, and typically contain about 20000 to 40000 units of lipase activity per dose unit, but their use has been associated with the development of fibrosing colonopathy in children with cystic fibrosis (see Effects on the Gastro-intestinal Tract, p. 2581.1). Such preparations are consequently not recommended for children in the UK and authorities there consider the total daily dose of pancreatic supplements for patients with cystic fibrosis should not exceed a lipase activity of 10000 units/kg.

Purified lipase preparations have also been used. A recombinant human bile-salt stimulated lipase is under investigation for the treatment of fat malabsorption in patients with exocrine pancreatic insufficiency and cystic fibrosis.

Pancreatin is also used to remove protein deposits from the surface of soft contact lenses (p. 1730.2).

Cystic fibrosis. Patients with cystic fibrosis (p. 177.2) suffer from pancreatic insufficiency and consequent malabsorption. Pancreatin or pancrelipase may therefore play a role in the management of the disorder, being taken before or with each meal or snack.

Generic substitution. Three patients with cystic fibrosis whose gastrointestinal symptoms had been well controlled with pancrelipase developed symptoms after substitution of generic pancrelipase for their previous brand.[1] The generic product had a different lipase content and was almost inactive at stomach pH *in vitro*, apparently because of a defective enteric coating. Different brands of pancrelipase may not be therapeutically equivalent and should not be routinely substituted.

1. Hendeles L, *et al.* Treatment failure after substitution of generic pancrelipase capsules: correlation with in vitro lipase activity. *JAMA* 1990; 263: 2459–61.

Pancreatitis. Pancreatitis is an inflammatory process affecting the pancreas. Acute pancreatitis comprises necrosis of pancreatic tissue occurring in an otherwise healthy gland, whereas chronic pancreatitis is the manifestation of pathological processes resulting in inflammation and progressive fibrosis of pancreatic tissue. Acute disease may be superimposed on a background of chronic pancreatitis.[1]

Acute pancreatitis is frequently associated with either biliary-tract disorders (such as gallstones or cholecystitis) or the intake of large amounts of alcohol, or less frequently with abdominal surgery, pancreatic trauma, hyperparathyroidism, hyperlipidaemia, or infection,[1-10] or rarely the adverse effects of drugs.[11] Endoscopic retrograde cholangiopancreatography (ERCP) is followed by acute pancreatitis in anywhere between 3 and 40% of patients,[1] although it may also be used successfully to treat acute pancreatitis associated with gallstones.[12]

Symptoms of acute pancreatitis include pain, which ranges from mild to extremely severe and which typically persists for several days, nausea and vomiting, ileus, and hypovolaemic shock. In severe disease, pulmonary, renal, and hepatic failure, encephalopathy, and death may ensue. A mortality rate of about 10% has been reported.

The management of acute disease is essentially supportive.[1-10] Adequate analgesia for pain is important (see Pancreatic Pain, p. 10.2); in mild cases, analgesia, adequate hydration, and temporary interruption of oral intake of food to 'rest' the pancreas may be adequate. In more severe disease enteral or parenteral nutrition may be needed,[1,6] although some[4,5,7-10,13] advocate enteral over parenteral nutrition because of potential complications with the latter. Adding probiotics to enteral feeds for prophylaxis against infectious complications in patients with predicted severe acute pancreatitis was not found to be of any benefit and might be associated with an increased risk of mortality.[14] Since most patients suffer from hypoxaemia it has been recommended that they should receive additional humidified oxygen by mask, with mechanical ventilation if blood gases indicate the development of severe pulmonary failure. Shock should be managed with blood or plasma, and electrolyte solutions, while insulin may be required for disturbances of glucose homoeostasis.

The value of other interventions is mostly doubtful. As an extension of the concept of 'pancreatic rest', inhibitors of pancreatic secretion including somatostatin or octreotide have been tried but without significant effect, while protease inhibitors such as aprotinin or gabexate mesilate have also proven disappointing,[2] perhaps because activation of pancreatic proteases (thought to play a significant role in pathogenesis) has already taken place by the time therapy is begun.[2] A meta-analysis[15] of studies using aprotinin or gabexate mesilate suggested that these might reduce mortality in moderate to severe acute pancreatitis. However, this conclusion has been criticised[16] based on weaknesses in the original studies and the criteria used for severity grading. Gabexate and somatostatin may have roles in the prevention of acute pancreatitis after ERCP,[17] but it remains difficult to identify which patients should be offered prophylaxis, since not all will develop the condition.[1,2] Furthermore, it has been suggested[18] that with improved techniques, the use of prolonged infusions of pharmacological prophylaxis against severe pancreatitis after ERCP may no longer be justified. Preliminary studies of the platelet-activating factor antagonist lexipafant for treatment of pancreatitis were initially promising but were not supported by subsequent larger studies.[3]

Although prophylactic antibacterials are often given, there has been some uncertainty about their value (see p. 196.2).

The role of surgery continues to be somewhat controversial; it is accepted for complications or when a potential surgical emergency exists.[1,2,4-7] Surgery to remove the gallbladder is usually delayed in severe episodes of acute, gallstone-related pancreatitis to allow resolution of the inflammatory process and improvement in the patient's nutritional state.[1] Early ERCP to clear an obstructed bile duct may reduce complications in patients with predicted severe pancreatitis, but does not reduce mortality.[12]

Chronic pancreatitis is frequently associated with high alcohol-intake,[1,19] although a tropical form[1] associated with malnutrition also exists, and some cases are idiopathic[20] or auto-immune.[21,22] Symptoms include recurrent episodes of pain (often less excruciating and of shorter duration than in acute pancreatitis) which normally become less severe and less frequent over the years with the inexorable progression of fibrosis. Loss of exocrine tissue eventually leads in many patients to pancreatic exocrine insufficiency, with malabsorption and steatorrhoea, and in some to diabetes mellitus due to islet cell loss. Other symptoms may include cholestatic jaundice, fatty degeneration of the liver, stenosis of the bile duct, and hepatic cirrhosis (although this may also be due to alcohol intake). It has been estimated that more than 50% of patients die within 20 years of diagnosis with those who continue to drink alcohol being at greatest risk. In some patients, chronic pancreatitis, especially that of hereditary origin, is a premalignant disorder.[1,19]

Current methods for diagnosis of chronic pancreatitis are to first use imaging techniques such as ultrasound or computed tomography (CT), but if those are equivocal or negative, then ERCP may be considered. Pancreatic function tests have also been used in the diagnosis of chronic pancreatitis. The secretin hormone stimulation test is the most sensitive test of pancreatic function but it is time-consuming, requires duodenal intubation, and is not widely available; the cholecystokinin test is similar but enzyme rather than hormone secretion is stimulated. Secretin is used alone or with cholecystokinetic drugs such as ceruletide, pancreozymin, or sincalide. Indirect noninvasive tubeless tests of pancreatic function are much simpler and more convenient to perform, and include the pancreolauryl test using fluorescein dilaurate, and the bentiromide (PABA) test in which metabolites excreted in the urine are taken as a measure of the enzyme-secreting activity of the pancreas. However, these are considered to be less reliable than direct hormone or enzyme stimulation tests. Pancreatic function tests are generally only reliable in patients with severe exocrine pancreatic insufficiency causing steatorrhoea and therefore have limited clinical use and are not routinely performed in practice. However, they might be helpful in the diagnosis of suspected chronic pancreatitis in patients who have normal imaging scans. Other noninvasive tests that have been used to diagnose chronic pancreatitis include faecal fat determination, and faecal measurement of pancreatic enzymes such as elastase and chymotrypsin, although these are limited by difficulties in sample collection and lack of sensitivity in early disease.[1,19,23,24]

Adequate analgesia with NSAIDs and opioids is essential for patients with chronic pancreatitis (see Pancreatic Pain, p. 10.2).[1,19] Nerve blocks of the coeliac plexus with phenol or alcohol have generally proved disappointing, although coeliac plexus blocks using corticosteroids and local anaesthetic may be effective.[1] However, response to nerve ablation procedures is often limited and of short duration.[20] Patients should be advised to abstain from alcohol, which can exacerbate the frequency and severity of painful episodes.[1,19] A low-fat diet is also recommended, or for patients who cannot tolerate oral intake, parenteral or enteral nutrition.[1,19,20] Steatorrhoea requires replacement of pancreatic enzymes with preparations of pancreatin or pancrelipase.[1,19,20] Because pancreatic enzymes are inactivated by gastric acid they may be taken after inhibitors of acid secretion[1,19] or with a sodium-containing antacid such as sodium bicarbonate (magnesium-, calcium-, and possibly aluminium-containing antacids may further interfere with fat absorption). Alternatively, enteric-coated enzyme preparations may be used.[20] In some patients with mild disease pancreatic enzyme replacement may also improve pain, although for this purpose only non-enteric coated preparations are effective.[1,19,20] However, a systematic review[25] found no strong evidence for recommending treatment with pancreatic enzymes for pain control or reduction of steatorrhoea, and no beneficial effect on quality of life was shown. There was also no evidence to suggest any advantage of enteric-coated over non-enteric-coated preparations. The authors concluded that sufficiently powered, randomised clinical studies comparing pancreatic enzymes with placebo are required before firm recommendations can be made. Supplements of fat-soluble vitamins are not normally necessary, but may be given intravenously

if required. Diabetes should be managed appropriately once steatorrhoea is under control.

Surgery, up to and including total pancreatectomy, has an important role in the relief of intractable pain, and may also be necessary for the management of complications.[1,19,20] Endoscopic decompression using contrast media containing prednisolone and ulinastatin has been reported to produce beneficial responses.[26]

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Adverse Effects and Precautions

Pancreatic enzyme supplements commonly cause gastrointestinal adverse effects such as abdominal discomfort and nausea and vomiting. They may also cause buccal and perianal irritation, particularly in infants. Colonic strictures (fibrosing colonopathy) have occurred, mainly in children with cystic fibrosis receiving high doses of pancreatin preparations; the use of high doses in patients with cystic fibrosis should preferably be avoided (see Effects on the Gastrointestinal Tract, below). Adequate hydration should be maintained at all times in patients receiving higher strength preparations.

Hypersensitivity reactions have been reported; these may be sneezing, lachrymation, or skin rashes. Hyperuricaemia or hyperuricosuria have occurred with high doses. There have been occasional reports of the contamination of pancreatin preparations with *Salmonella* spp.

Effects on folic acid. Pancreatic extract significantly inhibited folate absorption in healthy subjects and in pancreatic insufficient patients.[1] Testing *in vitro* showed that pancreatic extract formed insoluble complexes with folate. It was suggested[1] that patients being treated for pancreatic insufficiency should be monitored for folate status or given folic acid supplementation, particularly if pancreatic enzymes and bicarbonate (or cimetidine) were being used together in the treatment regimen.

1. Russell RM, *et al.* Impairment of folic acid absorption by oral pancreatic extracts. *Dig Dis Sci* 1980; 25: 369–73.

Effects on the gastrointestinal tract. *FIBROSING COLONOPATHY.* After the introduction of high-strength pancreatic enzyme preparations, there were reports[1-6] of colonic strictures in children with cystic fibrosis given these formulations, and the problem, now dubbed fibrosing colonopathy, was reviewed.[7,8] Fibrosing colonopathy has also been reported[9] in an adult who was not thought to have cystic fibrosis, but who had been taking high doses of pancreatic enzyme supplements, including 2 with methylacrylic acid copolymer (MAC) coatings, for 5 years after surgical removal of the pancreas.

The pathogenesis and aetiology of this condition still remain unclear. Dose-related thickening of the colon wall has been described,[10] and an inflammatory or immune-mediated mechanism has been suggested.[11,12] It has also been suggested that the type of preparation used may have a role. An analysis[13] of cases of fibrosing colonopathy occurring in the UK between 1984 and 1994 showed that there was a dose-related association between the high-strength preparations and this adverse effect although there was some criticism and debate surrounding the methodology of this particular analysis.[14-16] A subsequent case-control study[17] of patients in the US presenting between 1990 and 1994 concluded that there was a strong association between high daily doses of pancreatic enzymes, in any form, and the development of fibrosing colonopathy; no significant differences were seen between the various high- and low-strength preparations used. Re-analysis[18] of the UK data found a highly statistically significant association with the intake of preparations using MAC for enteric coating, but no evidence that a high intake of lipase in the absence of MAC was a risk factor for the disease. However, at least one case has been reported with a preparation that did not contain this material.[19]

As a result of these problems, high-strength preparations were withdrawn in the USA, while in the UK, the CSM recommended[20] that unless special reasons exist, patients with cystic fibrosis should not use high-strength pancreatin preparations, and that all patients treated with these products should be monitored carefully for gastrointestinal obstruction. The CSM later elaborated on these recommendations:[21] they advised that *Nutrizym 22, Pancrease HL,* and *Panzytrat 25 000* [now discontinued in the UK] should not be used in children with cystic fibrosis who were aged 15 years or less; that the total daily dose of pancreatic enzyme supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg; and that patients on any pancreatin preparation should be reviewed to exclude colonic damage if new abdominal symptoms or a change in symptoms occurred. Other risk factors identified were male sex, more severe cystic fibrosis, and the concomitant use of laxatives.[21] The US Cystic Fibrosis Foundation has made recommendations for the management of patients who do not respond adequately to moderate doses of pancreatic enzymes,[22] and similar recommendations have been made in the UK.[23]

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6. Pettei MJ, *et al.* Pancolonic disease in cystic fibrosis and high-dose pancreatic enzyme therapy. *J Pediatr* 1994; 125: 587–9.
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MOUTH ULCERATION. In 3 children taking preparations of pancreatic extracts (*Pancrex V powder, Pancrex V Forte*), severe mouth ulceration and angular stomatitis, causing dysphagia, loss of weight, and pyrexia, were attributed to digestion of the mucous membrane due to retention of the preparations in the mouth before swallowing.[1]

1. Darby CW. Pancreatic extracts. *BMJ* 1970; 2: 299–300.

Hypersensitivity. A successful desensitisation regimen has been described[1] for a child with cystic fibrosis who vomited within 1 to 2 hours after ingestion of pancreatic enzymes, suggestive of a type I hypersensitivity reaction.

1. Chamarthy LM, *et al.* Desensitization to pancreatic enzyme intolerance in a child with cystic fibrosis. Abstract: *Pediatrics* 1998; 102: 134–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/102/1/e13.pdf (accessed 14/07/06)

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

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Creon; Pancrecura; Pankreozym; Prolipase; Ultrase; ***Austral.***: Cotazym S Forte†; Creon; Panazyme†; Pancrease†; Panzytrat; ***Austria***: Kreon; Pancrin; Panzynorm; ***Belg.***: Creon; ***Braz.***: Cotazym†; Creon; Pancrease; Panzytrat; Polyzym; ***Canad.***: Bio-Zyme†; Cotazym; Creon; Pancrease; Ultrase; Viokase; ***Chile***: Creon; ***China***: Creon (得每通); *Cz.*: Gastrix†; Kreon; Pancreolan; Pangrol; Panzynorm; Panzytrat; ***Denm.***: Creon; Kreon; Pancrease; ***Fin.***: Creon; ***Fr.***: Creon; ***Ger.***: Cotazym; Fermento duodenal†; Helopan; Kreon; Lipazym; Mezym F; Ozym; Pangrol; Pankreatan; Panpur; Panzynorm forte-N; Panzytrat; Unexym mono; ***Gr.***: Creon; Pancrease; Panzytrat; ***Hong Kong***: Creon; ***Hung.***: Kreon; Mezym Forte; Neo-Panpur; Pangrol; Panzytrat; ***India***: Biopank; Creon; Digeplex; Enzar-HS; Festal N; Panstal N; Panzynorm-N; ***Irl.***: Creon; Nutrizym†; ***Israel***: Creon; Pancrease; ***Ital.***: Creon; Pancrex; ***Jpn***: LipaCreon; ***Malaysia***: Creon; ***Mex.***: Creon; Kenyna†; Opti-Free Supra Clens; Opti-Free; Pancrease; Trepetan; ***Neth.***: Creon; Pancrease HL; Pancrease†; Panzytrat; ***Norw.***: Creon; Kreon; Pancrease†; ***NZ***: Cotazym†; Creon; Pancrease; Pancrex; Panzytrat; ***Philipp.***: Creon; ***Pol.***: Kreon; Lipancrea; Neo-Pancreatinum; Pangrol; Panzytrat; ***Port.***: Kreon; ***Rus.***: Enzystal (Энзистал); Ermytal (Эрмиталь); Festal (Фестал); Gastenorm (Гастенорм); Kreon (Креон); Mezym Forte (Мезим Форте); Mikrazym (Микразим); Normoenzym Forte (Нормоэнзим Форте); Panzim (Панзим); Panzynorm (Панзинорм); Panzytrat (Панзитрат); Penzital (Пензитал); ***S.Afr.***: Creon; Pankrease†; Polyzym†; Viokase†; ***Singapore***: Creon; Norzyme; ***Spain***: Kreon; Papine†; ***Swed.***: Creon; Pancrease†; ***Switz.***: Creon; Panzytrat; ***Thai.***: Creon; ***Turk.***: Festal N; Kreon; ***UK***: Cleu-Zym; Creon; Nutrizym; Pancrease HL; Pancrex; ***Ukr.***: Enzibene (Энзибене); Kreasim (Креазим); Kreon (Креон); Mezym Forte (Мезим Форте); Micrazim (Микразим); Pancreasim (Панкреазим)†; Pangrol (Пангрол); Panzynorm (Панзинорм Форте-Н); ***USA***: Creon; Dygase; Enzymatic Cleaner†; Ku-Zyme HP†; Lapase; Lipram†; Opti-Zyme†; Palcaps†; PAN-2400†; Pancrease†; Pancreaze; Panocaps†; Pertzye; Tri-Pase; Ultrase†; Ultresa; Viokace; Viokase†; Vision Care Enzymatic Cleaner†; Zenpep; ***Venez.***: Orozim; Pankreon.

Multi-ingredient Preparations. *Arg.*: Arnol; Bibol Leloup; Bil 13 Enzimatico; Biletan Enzimatico; Biluen Enzimatico; Carbogasol Digestivo; Digenorflat; Digesplen; Dom-Polienzim; Enzybar; Facilgest; Faradil Enzimatico†; Gastridin-E; Homocisteon Compuesto; Moperidona Enzimatica†; Mosar Enzimatico; Pakinase; Pankreoflat; Pankreon Total; Polienzim; Praxis; Pronto Digest; Tridigestivo Soubeiran; ***Austral.***: Digestaid; Enzyme; Vegie Digestaid; ***Austria***: Helopanflat; Helopanzym; Intestinol†; Pankreoflat; Rennie Digestif; Wobenzym; ***Belg.***: Digestomen; ***Braz.***: Dasc†; Digecap-Zimatico; Essen; Pankreoflat; Peptopancreasi†; Plasil Enzimatico; Primeral; Proteobil; Sintozima†; ***Canad.***: Digesdyn; Digest; Digesta; Digestolax; Dipan†; Hepaticol; Lipozyme†; Multi-Zyme†; Pancre Zyme†; Wobenzym; ***Chile***: Combizym Compositum†; Digenil; Flapex E; Hepabil; Neopankreoflat; Nutrizima; ***China***: Combizym (慷彼申); Dages (达吉); Mite (泌特); YiMei (怡美); *Cz.*: Combizym Compositum†; Digestif Rennie†; Wobenzym; ***Ger.***: Chol-Arbuz NF; Enzym-Lefax; Meteozym; Pankreoflat†; Pascopankreat; Ventracid N†; Wobenzym N†; ***Hong Kong***: Appezym; Combizym; Digezym; Enzyme Co†; Enzyplex; ***Hung.***: Digestif Rennie†; Dipankrin; Pankreoflat; ***India***: Analiv; B-Zyme; Barozyme; Biohep; Digeplex-T; Dispeptal; Dizec; Enzar Forte; Enzolact; Enzovit; Farizym; Festal; Gaskit; Gesdyp; Hepa-Merz; Hepalon; Hepan-L; Hepasure; Hepator; Hepawin; Hiact-P; Kamozyme-EP; Kayliv; Laxzyme; Leno-EZ; Livtop; Medizyme; Merckenzyme†; Moret; Mumzyme; Omiliv; Omipan; Pankreoflat; Panlipase; Papytazyme; ***Indon.***: Benozym; Berzymplex; Cotazym Forte; Elsazym; Elsazym; Enzymfort; Enzyplex; Excelase-E; Flazymec; Gasflat;

Librozym Plus†; Librozym†; Nutriflam; Pankreoflat; Pankreon Comp; Pankreon for Children; Primperan Compositum; Tripanzym; Vitazym; Xepazym; *Israel*: Encypalmed; Pankreoflat†; *Malaysia*: Biotase; Enzyme Digest; Enzyplex†; *Mex.*: Difarben; Dixiflen; Espaven Enzimatico; Ochozim; Ononto; Pankreoflat; Plasil Enzimatico; Wobenzym; Zimeton; Zimotris; *Neth.*: Combizym†; *Norw.*: Combizym; *Philipp.*: Pankreoflat; Spasmo-Canulase; *Pol.*: Combizym; *Port.*: Colerin-P†; Espasmo Canulase†; Fermetone Composto; Helopanflat; Pankreoflat; *Rus.*: Biofestal (Биофесталь); Cholenzim (Холензим); Ipental (Ипентал)†; Pankreoflat (Панкреофлат); Phereshal (Фереспал); Wobenzym (Вобэнзим); *S.Afr.*: Pankreoflat; Spasmo-Canulase†; *Singapore*: Biotase; Enzyplex; *Spain*: Digestomen Complex; Nulacin Fermentos†; Pankreoflat; *Swed.*: Combizym Compositum†; Combizym; *Switz.*: Combizym Compositum; Combizym; Spasmo-Canulase; *Thai.*: Combizym Compositum†; Combizym; Enzymet; Gaszym; Pepsitase; Polyenzyme-I†; Polyenzyme-N; Proctase-P; *Turk.*: Fermento; Flaton; Hazmolin; Intestinol; Multanzim†; Pankreoflat; Pankreon Comp; Pankrodigest†; *UK*: Enzyme Digest; Enzyme Plus; *Ukr.*: Festal (Фестал); Wobenzym (Вобэнзим); *USA*: Bio-Zyme; Digepepsin; Digex†; Enzyme; Hi-Vegi-Lip; Ku-Zyme†; Kutrase†; Pangestyme†; Panplex 2-Phase; Similase Jr; *Venez.*: Combizym Forte; Festal Reformulado; Nutizym Compositum; Pankreon Compositum; Pankreosil; Stamyl; Wobenzym N.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Pancreatin Tablets; Pancreatin Granules;

USP 36: Pancreatin Tablets; Pancrelipase Capsules; Pancrelipase Delayed-release Capsules; Pancrelipase Tablets.

Pancreozymin *(BAN)*

CCK-PZ; Pancreocimina; Pankreotsymiini; Pankreozymin; Панкреозимин.

ATC — V04CK02.

ATC Vet — QV04CK02.

NOTE. The endogenous hormone is known as cholecystokinin (CCK).

Units

The potency of pancreozymin may be expressed as Crick-Harper-Raper units based on the pancreatic secretion in *cats* or as Ivy *dog* units based on the increase in gallbladder pressure. One Ivy dog unit is considered to be equivalent to about 1 Crick-Harper-Raper unit.

Profile

Pancreozymin is a polypeptide hormone prepared from the duodenal mucosa of *pigs*. When given by intravenous injection it causes an increase in the secretion of pancreatic enzymes and stimulates gallbladder contraction.

Pancreozymin has been used, usually with secretin, as a test for exocrine pancreatic function (see under Pancreatitis, p. 2580.2) and in the diagnosis of biliary-tract disorders; these tests generally involved duodenal intubation of the patient and examination of duodenal aspirate. Pancreozymin has also been used as an adjunct to cholecystography. Vasomotor reactions, abdominal discomfort, and hypersensitivity have been reported.

Biliary-tract disorders. It was concluded that cholecystokinin provocation testing was ineffective in predicting which patients with acalculous biliary pain would receive symptomatic relief from cholecystectomy in a study involving 58 patients.[1]

1. Smythe A, *et al.* A requiem for the cholecystokinin provocation test? *Gut* 1998; 43: 571–4.

Pangamic Acid

Pangámico, ácido; Пангамовая Кислота.

UNII — MPQ53A9F5C

Profile

The name pangamic acid has been applied variously to gluconic acid 6-[bis(diisopropylamino)acetate] ($C_{20}H_{40}N_2O_8$=436.5), gluconic acid, 6-ester with N,N-dimethylglycine ($C_{10}H_{19}NO_8$=281.3), gluconic acid, 6-ester with N,N-diisopropylglycine ($C_{14}H_{27}NO_8$=337.4), and a substance or mixture of substances isolated from apricot kernels and rice bran. It has also been known as 'vitamin B_{15}' although there is no evidence that pangamic acid is a vitamin. Preparations containing the vasoactive substance di-isopropylammonium dichloroacetate (p. 1359.1) have sometimes been described as pangamic acid or 'vitamin B_{15}'. There is much uncertainty about the identity of products sold in health food stores as 'vitamin B_{15}', pangamic acid, or sodium or calcium pangamate and different brands have been reported to have completely different compositions.

Claims for the activity of pangamic acid as a promotor of tissue oxygenation and its alleged value in many disorders have not been substantiated.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Deslatigan; Pulsor.

Multi-ingredient Preparations. *Arg.*: Varicofem; *Mex.*: B1-12-15; *Spain*: Policolinosil.

Homoeopathic Preparations. *Ger.*: Infi-Camphora.

Panthenol *(BAN, USAN, rINN)*

dl-Panthenol; Pantenol; Panthénol; Panthenolum; Пантенол; (±)-Pantothenyl Alcohol.

$C_9H_{19}NO_4$=205.3

CAS — 16485-10-2.

UNII — WV9CM0O67Z.

Pharmacopoeias. In *US*.

USP 36: (Panthenol). A racemic mixture of the dextrorotatory and laevorotatory isomers of panthenol. A white to creamy white, crystalline powder with a slight, characteristic odour. Freely soluble in water, in alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Dexpanthenol *(BAN, USAN, rINN)*

Dekspantenoli; Dekspantenolis; Dexpantenol; Dexpanthénol; Dexpanthenolum; Dextro-Pantothenyl Alcohol; Pantothenol; Provitamin B_5; Декспантенол.

(*R*)-2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutyramide.

$C_9H_{19}NO_4$=205.3

CAS — 81-13-0.

ATC — A11HA30; D03AX03; S01XA12.

ATC Vet — QA11HA30; QD03AX03; QS01XA12.

UNII — 1O6C93RI7Z.

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

Ph. Eur. 8: (Dexpanthenol). A colourless or slightly yellowish, hygroscopic, viscous liquid, or a white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. A 5% solution in water has a pH not greater than 10.5. Store in airtight containers.

USP 36: (Dexpanthenol). A clear, viscous, somewhat hygroscopic liquid, having a slight characteristic odour. Some crystallisation may occur on standing. Freely soluble in water, in alcohol, in methyl alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerol. Store in airtight containers.

Uses and Administration

Dexpanthenol is the alcoholic analogue of D-pantothenic acid (p. 2085.2). It has been given intramuscularly in doses of 250 or 500 mg to prevent or control gastrointestinal atony but its value has not been established. It has also been given by slow intravenous infusion.

Dexpanthenol and the racemate panthenol have been used topically in strengths of 2 or 5% for the treatment of various minor skin disorders. They are also included in some vitamin preparations.

References.

1. Kehrl W, Sonnemann U. Verbesserung der Wundheilung nach Nasenoperationen durch kombinierte Anwendung von Xylometazolin und Dexpanthenol. *Laryngorhinootologie* 2000; 79: 151–4.
2. Gehring W, Gloor M. Effect of topically applied dexpanthenol on epidermal barrier function and stratum corneum hydration: results of a human in vivo study. *Arzneimittelforschung* 2000; 50: 659–63.
3. Ebner F, *et al.* Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol* 2002; 3: 427–33.
4. Biro K, *et al.* Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. *Contact Dermatitis* 2003; 49: 80–4.
5. Rockmann H, *et al.* Anaphylaxis after dexpanthenol exposure by multivitamin tablets. *Clin Exp Dermatol* 2005; 30: 714–16.

Adverse Effects and Precautions

There have been a few reports of allergic reactions possibly associated with dexpanthenol. Dexpanthenol is contra-indicated in haemophiliacs and in patients with ileus due to mechanical obstruction.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Recugel; *Austral.*: Bepanthen; *Austria*: Bepanthen; Corneregel†; Panto Liquid; Pantothen; *Braz.*: Bepantol; Cicatenol; Dexpantol; Neopantol; Pantodex; *Chile*: Bepantol; *Cz.*: Bepanthen; Panthenol; *Fin.*: Bepanthen; *Fr.*: Bepanthen; Bepanthene; BepanthenSensicalm; *Ger.*: Bepanthen; Corneregel; Maroldermt†; NasenSpray Panthenol; Nasic-cur; Ottiven mit Dexpanthenol†; Pan-Ophtal; Panthenol; *Gr.*: Bepanthene; Corneregel; *Hong Kong*: Corneregel; *Hung.*: Bepanthen; Corneregel; Panthenol; *Indon.*: Bepanthen; Pasquam; Tentalux; *Israel*: Bepanthen; Dermacalm; Neocutan; *Ital.*: Bepanten; *Mex.*: Bepanthen; Corneregel; *NZ*: Bepanthen; *Philipp.*: Corneregel; *Pol.*: Bepanthen; Corneregel; Dermopanten; *Port.*: Bepanthene; *Rus.*: Bepanthen (Бепантен); Corneregel (Корнерегель); Moreal-Plus (Мореаль-Плюс); Pantenol (Пантенол); Panthenol (Пантенол); Panthoderm (Пантодерм); *S.Afr.*: Bepanthen†; *Singapore*: Bepanthen; *Spain*: Bepanthene; *Switz.*: Bepanthen; Bepanthene; *Thai.*: Bepanthen; *Turk.*: Armathene; Bepanthene; Bepantol†; Pantebiol; Pantenol†; Pantomed; *UAE*: Dexipan; *UK*: Bepanthen; *Ukr.*: Bepanthen (Бепантен); Corneregel (Корнерегель); Depantol (Депантол); Panthecream (Пантекрем); Panthenol (Пантенол Спрей); *USA*: Ilopan; Panthoderm.

Multi-ingredient Preparations. *Arg.*: Aftersun; Amplus; Dermocridin; Dermvien; Heduline; Hydratone; Lociherp Liposomas Vitaminado; Macbirs; Mucobase; Novofarma; Rain-LY; Sebulex; Talowin; *Austral.*: Macro Natural Vitamin E Cream; Sebirinse; *Austria*: Bepanthen Plus; Bepanthen†; Colda; Coldistan; Dolobene; Keratosis forte; Keratosis; Nasic; Oleovit; Siccaprotect; Sigman-Haustropfen; Venobene; *Belg.*: Algi-Cool†; Purigel NF; *Braz.*: Capel; Dolobene†; Esmalfort; Ferrocomplex; Fisioativ; Naridrin; Nariflux; Uvless; *Chile*: Aftagel Bucal; Benutrex 1000†; Biopiel; Cicapost; Diencil; Eucerin Correctora Anti-Espinillas; Eucerin Micropigmentos; Eucerin Piel Grasa†; Pantoderm-A†; Pomada Vitaminica; Queratopil; Ureadin Facial Antiarrugas; Ureadin Rx DB; Ureadin Rx RD; Urealeti; Vitis Encias Colutorio; Vitis Encias Pasta; *China*: Dolobene (瑞乐平); Xin Le Dun (新乐敦); *Cz.*: Bepanthen Plus; Dolobene; Nasic; Panlid†; Siccaprotect; *Fin.*: Oftan A-Pant; Pantyson; Wicaran; Wicarba; *Fr.*: Bebebiafine Anti-Rougeures; Calmobrul; Cicactive; Herpclair; *Ger.*: Bepanthen Antiseptische; Bepanthen Augentropfen; Dispatenol; Dolobene†; GeloBacin; Hewekzem novo N; Hydro Cordes; Hylo-Care; InfectoGripp; Lipo Cordes; Nasic; PC 30 V; Remederm; Saseem; Siccaprotect; Siozwo San; *Gr.*: Aquasol A; Nasosyn; Novaquasol-A; *Hong Kong*: Dolobene†; Mar Plus; Pregnacare; Sebirinse; *Hung.*: Alksebor; Antikeloid; Aurobin; Bepanthen Plus; Dolobene; Pelsano Med; Phlogosam; *India*: Acnic-S; Alfariz; Alprovit DPS; Altone; Altrazyme; Alvit; Ampiro; Aneudox-12; Anvital DPS; Anzykair; Asiplex; Astyfer; Aviton; B-12; B-12; Cherrytone; Climdan; Climdan; Focobal Plus; Meconerv; Mego-XL; Mericobal; Nurokind Plus; Nutrared; Optineuron; Sioneuron; Vitneurin; *Indon.*: Apecur; Bevita; Brainvit; Confortin; Romilar Expectorant; Skintex†; *Israel*: Bepanthen Plus; Kamil Blue; Kamil Blue; Neocutan Silver; Panthisone†; Pedisol†; *Ital.*: Alfa Acid; Biomineral 5-Alfa Shampoo; Biorag; Gastrotuss; Hylo-Care; Keto Z; Lenirose; Parogencyl; Recugel; Respifree Nasale; Rinopanteina; *Malaysia*: Bepanthen Plus; Hairmonius; Mar Plus; Palmer's Cocoa Butter Formula Nappy Rash Ointment; Palmer's Cocoa Butter Formula Nursing Cream; pH Care; *Mex.*: Aloemagnolia; Cetopic; Emolin Neo; Nutrem; Salilex; *Neth.*: Prunacolon; Prunasine; *NZ*: Sebirinse; *Philipp.*: Ascovit-C†; Megavit; pH Care; Remederm†; Sebo Fluid†; Suplenex; *Pol.*: Acodin; Alantan-Plus; Bepanthen Plus; Dolobene†; *Port.*: Bepanthene Plus; Bepanthene†; Bexident; Cicapost; Efluvium Anti-seborreico†; Lactigriet; Nutraisdin; Nutraisdin; Ureadin 10 Plus; *Rus.*: Aurobin (Ауробин); Bepanthen Plus (Бепантен Плюс); Depanthol (Депантол); Dolobene (Долобене); Hepatrombin (Гепатромбин); Hylozar-COMOD (Хилозар-КОМОД); Venolife (Венолайф); *S.Afr.*: Broncol†; *Singapore*: pH Care Intimate Wash; *Switz.*: Alphastria; Assan rem; Bepanthen Plus; Bepanthene Plus; Carbamide + VAS; Dermacalm-d; Dolobene; Fluimare Plus; Gorgonium; Hylo-Care; Lyman; Nasic; Nasmer 3plus; Nasmer free; No Pic; Nose Fresh au D-panthenol; Osa Gel de dentition; Parapic†; PC 30 V; Pelsano; Pigmanorm; Rhinomer mini; Siccalix; Siccaprotect; Sportium; Sportusal Spray sine heparino; Sportusal; Stilex; Turexan Capilla†; Unathene†; Undex†; Venucreme; Venugel; *Thai.*: Bepanthen First Aid; Mar Plus; Romilar; *Turk.*: Bepanthene Plus; Numis; Pantenol Plus; Rinopanteina; Siccaprotect; Stilex; *UK*: Allerclear; Hylo-Care; Oilatum Scalp Intensive; Uvistat Eye Drops; Vipsogal; *Ukr.*: Aurobin (Ауробин); Bepanthen Plus (Бепантен Плюс); Dolobene (Долобене); Pitoval Shampoo (Фитовал шампунь); Hepathrombin (Гепатромбин); Panthestin (Пантестин); Panthevenol (Пантевенол); Phytobene (Фитобене); Rjativnik (Ртутяник); Venohepanol (Веногепанол); *USA*: Aquaphor Healing Ointment; *Venez.*: Cepin; Diadex; Pantonic.

Pharmacopoeial Preparations

USP 36: Dexpanthenol Preparation; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Water-soluble Vitamins Capsules; Water-soluble Vitamins with Minerals Capsules.

Papain ⊗

EC 3.4.22.2; Papaina; Papaína; Papayotin; Папаин.

CAS — 9001-73-4.

ATC Herb — HA09AA5002 (Carica papaya: extract).

UNII — A236A06Y32.

Pharmacopoeias. In *US*.

USP 36: (Papain). A purified proteolytic substance derived from *Carica papaya* (Caricaceae). It contains not less than 6000 USP units per mg. A white to light tan, amorphous powder. Soluble in water, the solution being colourless to light yellow and more or less opalescent; practically insoluble in alcohol, in chloroform, and in ether. pH of a 2% solution in water is between 4.8 and 6.2. Store in airtight

containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Units

USP 36 defines the USP unit of papain activity as the activity that releases the equivalent of 1 microgram of tyrosine from a specified casein substrate under the conditions of the assay, using the enzyme concentration that liberates 40 micrograms of tyrosine per mL of test solution.

One FIP unit of papain is defined as the enzyme activity which under specified conditions hydrolyses 1 micromol of *N*-benzoyl-L-arginine ethyl ester per minute.

The Warner-Chilcott unit, based on the quantity of enzyme required to clot 2.64 microlitre of milk substrate in 2 minutes at 40 degrees, under specified conditions, has also been used for papain.

Uses and Administration

Papain consists chiefly of a mixture of papain and chymopapain, proteolytic enzymes that hydrolyse polypeptides, amides, and esters, especially at bonds involving basic amino acids, or leucine or glycine, yielding peptides of lower molecular weight. It is used with urea as a topical debriding agent. It is also used for the removal of protein deposits from the surface of soft contact lenses (p. 1730.2).

Preparations of papain, alone or combined with antibacterial agents and/or other substances, have been taken orally for their supposed anti-inflammatory properties, and it has also been used as an ingredient of various mixtures claimed to aid digestion.

Papain is widely used as a meat tenderiser and in the clarification of beverages.

Malignant neoplasms. Papain has been included in proteolytic enzyme preparations used in oncology to reduce the adverse effects of chemotherapy and radiotherapy. Although the number of clinical studies on which to judge efficacy is limited, a review[1] of such studies suggested that systemic enzyme therapy might be beneficial. Clinical studies have used a preparation containing papain, trypsin, and chymotrypsin in a weight ratio of 5:2:2, and the beneficial effect seems to be based on its anti-inflammatory potential.

1. Leipner J, Saller R. Systemic enzyme therapy in oncology: effect and mode of action. *Drugs* 2000; 59: 769–80.

Adverse Effects

Hypersensitivity reactions have occurred.

Effects on the eyes. Ocular and periorbital angioedema occurring within 4 hours of use of a contact lens cleansing solution containing papain has been reported.[1]

1. Bernstein DL *et al.* Local ocular anaphylaxis to papain enzyme contained in a contact lens cleansing solution. *J Allergy Clin Immunol* 1984; 74: 258–60.

Oesophageal perforation. Extensive destruction of the oesophageal wall, with perforation, resulted from the use of a papain suspension given to treat an obstruction caused by impacted meat.[1] The patient had been given 1.2 g of papain over a 12-hour period. Ten days after a thoracotomy, the descending thoracic aorta ruptured, and she died from haemorrhage.

1. Holsinger JW, *et al.* Esophageal perforation following meat impaction and papain ingestion. *JAMA* 1968; 204: 734–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Stop Itch; *Canad.*: Digest Aid†; Digestol; Solarcaine Stop Itch†; *Chile*: Papenzima; *Hong Kong*: Eurolase; *Malaysia*: Beazyme; *NZ*: Stop Itch; *Rus.*: Caripazym (Карипазим); *USA*: Allergan Enzymatic†; ProFree†.

Multi-ingredient Preparations. *Arg.*: Bucal Tac Whitening Gel; Butimerin; Docechol; Homocisteon Compuesto; Opoenterol; Pankreon Total; Solustres; *Austral.*: Betaine Digestive Aid; Bio-Disc†; Digestaid; Enzyme; Tresos B PluSe; Vegie Digestaid; *Austria*: Rennie Digestif; Wobe-Mugos; Wobenzym; *Belg.*: Digestomen; *Canad.*: Digesdyn; Digest; Digestolax; Multi Enzyme†; Multi-Zyme†; Proteozyme Forte; Wobenzym; *China*: Dages (达吉); *Cz.*: Digestif Rennie†; Wobenzym; *Ger.*: Wobenzym N†; *Gr.*: Lysopaine; Sopain-Plus; *Hong Kong*: Appezym; Caricose†; Digezym; Enzyme Co†; *Hung.*: Digestif Rennie†; *India*: Bestozyme P; Bestozyme; Bestozyme; Catalyd; Catazyme-P; Dipep; Eaze; Enzofast; Gastrozyme; Glozyme; Intrazyme; Jayzyme; Lac-B; Laxzyme; Merispas; Merozyme-C; Neopeptine; Neopeptine; Neopeptine; Nutrozyme; Nutrozyme; Papytazyme; Unienzyme; *Indon.*: Papaven†; *Malaysia*: Enzyme Digest; Pepfiz; *Mex.*: Digenor Plus; Wobe-Mugos; Wobenzym; *Pol.*: Carident; *Rus.*: Pepfiz (Пепфиз); Unienzyme с MPS (Юниэнзим с МПС); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); *Singapore*: Stop-Itch Plus; *Spain*: Digestomen Complex; Lizipaina; *Switz.*: Lysopaine†; *Thai.*: Pepfiz; Pepsitase; Polyenzyme-I†; *UK*: Enzyme Digest; Herbal Indigestion Naturtabs; Indigestion and Flatulence; *Ukr.*: Digestin (Дигестин); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); *USA*: Accuzyme†; AllanEnzyme†; AllanfillEnzyme†; Bio-Zyme; Gladase-C†; Gladase†; Kovia†; Panafil-White†; Panafil†; Papaya Enzyme; Papfyll; Ziox†; *Venez.*: Wobenzym N.

Pharmacopoeial Preparations
USP 36: Papain Tablets for Topical Solution.

Paradichlorobenzene

Dichlorbenzol; Paradiclorobenceno; Пара-дихлорбензол.
1,4-Dichlorobenzene.
$C_6H_4Cl_2$=147.0
CAS — 106-46-7.
UNII — D149TYB5MK.

Profile

Paradichlorobenzene has general properties similar to those of orthodichlorobenzene (see p. 2578.1) but is considered to be less toxic. It is present in several preparations intended for the removal of ear wax (see p. 1836.3). It has been used as a furniture preservative and in mothballs and lavatory deodorant blocks. Abuse of preparations containing paradichlorobenzene has been reported.

Abuse. Neurocutaneous symptoms have been reported[1] in 2 18-year-old twin girls after abuse of mothballs by inhaling the fumes, and in one twin, also chewing the mothballs. Once they stopped, both sisters recovered completely within 3 to 6 months depending on their previous level of abuse. Intermittent nasal inhalation and ingestion of mothballs over many years led to toxic leukoencephalopathy in a 32-year-old woman.[2] Her symptoms improved when she had no access to mothballs but reappeared when abuse resumed. In another patient it was suggested that neurotoxicity after abuse of mothballs may have been due to a withdrawal syndrome rather than direct toxicity of paradichlorobenzene.[3] Haemolytic anaemia has also been associated with ingestion of mothballs.[4]

1. Peuillet L *et al.* Twin girls with neurocutaneous symptoms caused by mothball intoxication. *N Engl J Med* 2006; 355: 423–4.
2. Kumar N, *et al.* Mothball mayhem: relapsing toxic leukoencephalopathy due to *p*-dichlorobenzene neurotoxicity. *Ann Intern Med* 2009; 150: 362–3.
3. Cheong R, *et al.* Mothball withdrawal encephalopathy: case report and review of paradichlorobenzene neurotoxicity. *Subst Abus* 2006; 27: 63–7.
4. Sillery JJ, *et al.* Hemolytic anemia induced by ingestion of paradichlorobenzene mothballs. *Pediatr Emerg Care* 2009; 25: 252–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Cerumol; *Canad.*: Cerumol; *India*: Ceruklin; Clearwax; Desol; Despol; Dewax; Fastwax; Nayawax; Nill-O-Wax; Otoclean; Otorex; Parabec; Waxolve†; *Irl.*: Cerumol; *Israel*: Cerumol; *Malaysia*: Cerumol; *Port.*: Otocerll; *S.Afr.*: Cerumol; *Singapore*: Cerumol; *Switz.*: Cerumenol; *UK*: Cerumol.

Paraphenylenediamine

Parafenilendiamina; Парафенилендиамин.
p-Phenylenediamine; 1,4-Benzenediamine.
$C_6H_4(NH_2)_2$=108.1
CAS — 106-50-3.
UNII — U770QIT64J.

NOTE. Commonly known in the hairdressing trade as *'para'*. 'PPD' is an abbreviation sometimes used for paraphenylenediamine, which should not be confused with tuberculin purified protein derivative (see Tuberculins, p. 2635.3), which is also referred to by the same abbreviation.

Profile

Paraphenylenediamine is widely used in permanent hair colour preparations. However it is a potent contact allergen and EU legislation restricts its concentration in the finished product to a maximum of 6% calculated as free base. Both type I and type II reactions occur and symptoms usually present as dermatitis on the face or hands. More severe reactions can lead to angioedema; anaphylaxis has also been reported. Systemic symptoms similar to those after ingestion (see below) may also occur following absorption through intact skin. For references to hypersensitivity after skin tattoos with henna that was mixed with paraphenylenediamine, see below.

Application of tints to the eyelashes or eyebrows may produce blepharoconjunctivitis, eye oedema, and eye pain, with progression to facial oedema and dermatitis, lachrymation, photophobia, uveitis, and keratitis in severe cases. Corneal necrosis has led to blindness. In some countries, use of paraphenylenediamine in eyelash or eyebrow tints is banned.

Early symptoms after ingestion of paraphenylenediamine are vomiting and abdominal pain. Severe oedema of the face and oropharynx can lead to life-threatening obstruction of the airways. Other symptoms may include hypotension or hypertension, tachycardia, hepatotoxicity, renal failure, metabolic acidosis, methaemoglobinaemia, rhabdomyolysis, tremor, convulsions, and coma; multisystem failure may be fatal.

Some studies have linked hair dyes with mutagenicity and carcinogenicity, although such findings have often been refuted. In the EU, legislation controls which substances may be used in hair dye products.

Paraphenylenediamine is also used in the textile and photographic industries.

Hypersensitivity. Paraphenylenediamine is added to natural henna (p. 2525.1) to darken it (known as black henna) for use in temporary skin tattoos. However, there have been reports of the paraphenylenediamine component producing hypersensitivity reactions,[1-9] permanent skin pigment changes,[6,9] and also cross-sensitisation to paraphenylenediamine-containing hair dyes[2,6-9] and textile dyes;[6,9] there is also the possibility of sensitisation to other allergens such as natural rubber latex.[9]

1. Brancaccio RR, *et al.* Identification and quantification of *para*-phenylenediamine in a temporary black henna tattoo. *Am J Contact Dermat* 2002; 13: 15–18.
2. Marcoux D, *et al.* Sensitization to para-phenylenediamine from a streetside temporary tattoo. *Pediatr Dermatol* 2002; 19: 498–502.
3. Neri I, *et al.* Childhood allergic contact dermatitis from henna tattoo. *Pediatr Dermatol* 2002; 19: 503–5.
4. Bowling JCR, Groves R. An unexpected tattoo. *Lancet* 2002; 359: 649.
5. Leggiadro RJ, *et al.* Temporary tattoo dermatitis. *J Pediatr* 2003; 142: 586.
6. Matulich J, Sullivan J. A temporary henna tattoo causing hair and clothing dye allergy. *Contact Dermatitis* 2005; 53: 33–6.
7. Sosted H, *et al.* Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; 54: 87–91.
8. Redlick F, DeKoven J. Allergic contact dermatitis to paraphenylendiamine in hair dye after sensitization from black henna tattoos: a report of 6 cases. *CMAJ* 2007; 176: 445–6.
9. Sonnen G. Type IV hypersensitivity reaction to a temporary tattoo. *Proc (Bayl Univ Med Cent)* 2007; 20: 36–8.

Poisoning. References.

1. Ashraf W, *et al.* Systemic paraphenylenediamine (PPD) poisoning: a case report and review. *Hum Exp Toxicol* 1994; 13: 167–70.
2. Lifshits M, *et al.* Fatal paraphenylenediamine (hair dye) intoxication in a child resembling Ludwig's angina. *J Toxicol Clin Toxicol* 1993; 31: 653–6.
3. Anuradha S, *et al.* Acute renal failure following para-phenylenediamine (PPD) poisoning: a case report and review. *Ren Fail* 2004; 26: 329–32.
4. Kallel H, *et al.* Clinical manifestations of systemic paraphenylene diamine intoxication. *J Nephrol* 2005; 18: 308–11.
5. Brahmi N, *et al.* Acute myocarditis and myocardial infarction induced by paraphenylenediamine poisoning. Interest of angiocoronarography. *Int J Cardiol* 2006; 113: E93–E95.
6. Bhargava P, Matthew P. Hair dye poisoning. *J Assoc Physicians India* 2007; 55: 871–2.
7. Abidi K, *et al.* Myocardial lysis in a fetus induced by maternal paraphenylenediamine poisoning following an intentional ingestion to induce abortion. *Hum Exp Toxicol* 2008; 27: 435–8.
8. Soni SS, *et al.* Systemic toxicity of paraphenylenediamine. *Indian J Med Sci* 2009; 63: 164–6.

Paratoluenediamine

Paratoluendiamina; Пара-толуолдиамин.
2-Methyl-1,4-phenylenediamine.
$C_7H_{10}N_2$=122.2
CAS — 95-70-5.
UNII — 24JQ8Z0RJU.

Profile

Paratoluenediamine is used in hair colour preparations.

Like paraphenylenediamine, above, paratoluenediamine may be associated with sensitivity reactions.

Parsley

Perejil; Persil; Persil, racine de (parsley root); Petersilie; Petrželový kořen (parsley root); Petroselini Radix (parsley root); Petroselinum; Петрушка.
ATC Herb — HA03AW5045 (Petroselinum crispum: *root*); *HG02WB5006* (Petroselinum crispum: *fruit*); *HG04BW5026* (Petroselinum crispum: *fruit*); *HG04BW5027* (Petroselinum crispum: *root*).
UNII — 58FMD0Q0EV (Petroselinum crispum *top*); *1WZA4Y92EX* (Petroselinum crispum); *030FN29S9H* (Petroselinum crispum *root*).

Profile

Parsley (*Petroselinum crispum*, Umbelliferae) is used in herbal medicine, where it is mainly given as a diuretic. It is also used as a culinary herb and flavouring.

Parsley oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Odo-fre.

Multi-ingredient Preparations. *Arg.*: Daily Nutrilite; Parselenium B; *Austral.*: Extralife Fluid-Care†; Hair Skin & Nails; Odourless Garlic; *Canad.*: Cellutex; Diuretic Formula; Herbal Diretic; Herbal Diuretic†; Herbal Diuretic; Saw Palmetto Formula†; *Cz.*: Species Urologicae Planta; Urologicka Cajova Smes; *Fr.*: Alibi; Oropur; *Ger.*: Asparagus-P; *India*: Nutiva-Lyco; *Rus.*: Herbion Urological Drops (Гербион Урологические Капли); *UK*: AsPar-Aid; Athera; Pre-bre; Mixed Vegetable Tablets; Modern Herbals Menopause; *Ukr.*: Herbion Drops for the Kidneys and Bladder (Гербион Капли для Почек и Мочевого Пузыря)†; Nephrocare (Нефрокеа); Tazalok (Тазалок); Urocran (Урокран); Uronephron (Уронефрон).

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Fr.*: Santalum Complexe No 30†; *Ger.*: Cysto Hevert; Hewecyst Blasen-Nieren†; Pascorenal N; *Neth.*: Cystilite; Homeocare Uro.

Parsley Piert

Alchémille des Champs; Alquimila arvense; Aphanes; Gewöhnlicher Acker-Frauenmantel; Невзрачница Полевая (*Aphanes arvensis*).

Profile

Parsley piert, the aerial parts of *Aphanes arvensis* (*Alchemilla arvensis*) (Rosaceae) has astringent, diuretic, and demulcent properties. It is used for urinary-tract disorders, including renal and urinary calculi.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Kontryhelova Nat.

Multi-ingredient Preparations. *Cz.*: Fytokliman Planta; *UK*: Backache Relief; Diuretabs; HRI Water Balance.

Passion Flower

Burucuyá; Flor de la pasión; Golgotavirág hajtásvég; Granadilla; Grenadille; Kärsimyskukka; Maracuyá; May-pop; Mučenková nať; Pasifloru žolė; Pasiflora; Pasionari; Pasionaria; Passiflora; Passiflorae Herba; Passiflore; Passionsblomma; Passionsblumenkraut; Страстоцвет Мясо-красный.

CAS — 8057-62-3 (passion flower extract).

ATC Herb — HN05CM5019 (Passiflora incarnata: *herb*).

UNII — CLF5YF511O (Passiflora incarnata *top*); *K8F3G29S6Z* (Passiflora incarnata *flower*); *SF2061BG4P* (Passiflora incarnata *fruit*); *SY49TH8VUA (passion flower extract).*

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

Ph. Eur. 8: (Passion Flower). The fragmented or cut, dried aerial parts of *Passiflora incarnata*; it may also contain flowers and/or fruits. It contains not less than 1.5% of total flavonoids expressed as vitexin ($C_{21}H_{20}O_{10}$ = 432.4), calculated with reference to the dried drug. Protect from light.

Profile

Passion flower is reputed to have antispasmodic and sedative properties and has been used as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture.

Homoeopathy

Passion flower has been used in homoeopathic medicines under the following names: Passiflora incarnata; Passiflora; Passi. in.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sedante Noche; *Austria*: Pascoflair; Passiflorin; *Belg.*: Sedanxio; Sedistress; *Braz.*: Acalmil; Sintocalmy; Tensart; *Ger.*: Hoggar Balance; Kytta-Sedativum fur den Tag; Pascoflair; Passidon; Passiflora Curarina; *Hung.*: Naturest; *Pol.*: Passiflor; *Rus.*: Novo-Passit (Ново-Пассит); *Spain*: Pasang; *Switz.*: A Vogel Gouttes relaxantes; Dormodyn; Valverde Apaisement; *Turk.*: Alora; Poliflorin; Sedaflora; *UK*: DiaPassion; Modern Herbals Sleep Aid; Natracalm; Naturest; Nodoff; Pascoe Calm; Phytocalm; RelaxHerb; *Ukr.*: Alora (Алора); *Venez.*: Floral Pas.

Multi-ingredient Preparations. *Arg.*: Armonil; Calmtabs; Nervocalm; Passacanthine; Phytocalm; SDN 200; Sedanat†; Sedante Dia; Serenil; Sigmasedan; Valeriana Compuesta; Yerba Diet; *Austral.*: Advanced Restless Leg Care; Aloe Vera Plus; Calmo†; Euphorbia Complex†; Executive B Stress Formula; Executive B†; Executive Sleep Formula; Extralife Sleep-Care†; Herbal Rest & Relax; Humulus Compound; Natural Deep Sleep†; Nervatona Calm; Nervatona Focus; Passionflower Plus†; Sleep Easy; Sleep Naturally; Tranquil Night; Valerian Complex; *Austria*: Alpinamed Passelyt; Nervenruh; Neurapas; Passedan; Sedogelat; Wechseltee St Severin; *Belg.*: Sedinal; Seneuval; *Braz.*: A Saude da Mulher; A Saude da Mulher; Bronquiogen†; Calman; Calmapax; Calmiplan; Floriny; Pasalix; Pasic; Passaneuro; Passaneuro; Passiflorine; Ritmoneuran; Sedantol; Serenus; Sominex; Vagostesyl; *Canad.*: Calmane; Calmane; Detente†; Dormane Plus; Dormane Tisane; Dormane; Herbal Insomnia†; Myoplex†; Natural HRT Nightime; Nervinat; Phytocalm†; Relax Plus; Relaxant; Relaxol; Salusan†; Sleep Relax; *Chile*: Armonyl Nocturno; Armonyl; Melipass; Recalm†; *Cz.*: Novo-Passit; Passedan†; Passit; *Fr.*: Biocarde; Boribel Tisane No 8†; Calmiflorine†; Calmotisan†; Euphytose; Fibromyalgine Fort; Fibromyalgine; Mediflor Tisane Calmante Troubles du Sommeil No 14; Natudor; Neuroflorine†; Neuropax†; Nocvalene†; Panxeol†; Passiflorine; Passinevryl†; Plenesia; Provencale No 4†; Santane N; Sedatif Tiber†; Sympavagol†; Tisane Provencale no 4†; *Ger.*: Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Kytta-Sedativum; Moradorm S; Neurapas; Passin; Phytonoctu; Seda-Plantina N; Tornix; Valeriana Beruhigungsdragees; Vivinox Day; *Gr.*: Passiflorine; Passinevrol; Vivinox; *Hung.*: Habstal-Nerv N; Sedogelat; *Indon.*: Slip-iZZZ†; *Irl.*: Avena Sativa Comp; Quiet Life; *Israel*: Calmanervin; Calmanervin; Nerven-Dragees; Passiflora Compound†; Passiflora; *Ital.*: Actenacol; Anevrasi; Biocalm; Calmason; Controller; Dormil; Fitosonno; No Gas Enzimi; Noctis; Parvisedtl; Passiflorine; Saniquiet; Sedatol; Sedatol; Sedopuer F; Vagostabil Junior; *Mex.*: Ifupasil; Pasinordin; *Neth.*: Plantival; *Philipp.*: Sleepasil; *Pol.*: Nervendragees; Nerwonal; Passibil; Passispasmin; Passispasmol†; Psychotonisol†; Valused; *S.Afr.*: Avena Sativa Comp†; Biral†; *Spain*: Netisum; Neurapas; Passiflorine; Sedonat; Valdispert Complex; Valeriana Leo; Valrelax†; *Switz.*: Circulan†; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Dragees pour le coeur et les nerfs; Femisan; Gouttes pour le coeur et les nerfs; Passiflor; Relaxane; Relaxo; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane antirhumatismale; Tisane calmante pour les enfants; Valverde Coeur; Valverde Detente dragees; *UK*: Anased; Avena Sativa Comp; Bio-Strath Valerian Formula; Botanova; Chamomile Blend; Daily Tension & Strain Relief; DiaDay & Night; DiaNight Plus; DiaRelax; DiaSleep Plus; Gerard House Serenity; Goodnight; Herbal Pain Relief; HRI Night; Kalms Sleep; Modern Herbals Stress; Napiers Herbal Stress & Sleep Aid; Niteherb Plus; Nodoff; Nytol Herbal; PMT Formula; Quiet Life; Quiet Nite; Quiet Tyme; Relax B+; Slumber; Sominex Herbal; SuNerven; Valerian Passiflora and Hops; *Ukr.*: Central-B (Централ-Б); Herbastress (Гербастресс); Klimased (Климасед); Novo-Passit (Ново-Пассит); Persen Cardio (Персен Кардио); *USA*: PowerSleep; *Venez.*: Equaliv; Lupassin; Pasidor; Pasifluidina; Passiflorum; Rendetil; Sedival.

Homoeopathic Preparations. *Austral.*: Calm; Nervatona Calm; Nervatona Focus; Sleep & Insomnia Relief; Smoke Eze; *Austria*: Avena Rihom Komplex†; *Canad.*: Calms Forte; Calsom†; Comp-Drops 1 Stress†; Comp-Drops 7 Sleepless†; Homeo-Form I†; Homeogene 46; Hylands Formula C; Hylands Formula CF; Insomnia Passiflora†; Insomnia; Passiflora Complex†; Quietude; Sedilor†; Spascupreel; *Cz.*: Sedalia; Spascupreel S†; *Fr.*: Boripharm No 3; Boripharm No 41; Calmodren; Homeogene 46; Passiflora Compose; Passiflora GHL; Quietude; Slipeol†; *Ger.*: Alho-Sedosan; Avena sativa comp†; Calmvalera; Cefaneuro; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; Dormosyx; dysto-loges N; dysto-loges S; Infinerval; Nervo-Plantin†; Nervoid N; Nervoregin H; Nervoregin; Neurexan; Neuro-Ginsan N; Neuroselect; Pascolibrin; Passiflora Complex†; Seda-Do; Sedakatt; Spascupreel; Tondinel H; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Hung.*: Spascupreel; *Neth.*: Homeocare Nervo; Hyperilite; Quietude†; Weleda Avena Valeriana; *Rus.*: Nux Vom-Plus (Нукс Вом-Плюс); Passidorm (Пассидорм); Tabacum-Plus (Табакум-Плюс); Valeriana-Plus (Валериана-Плюс); *Switz.*: Nelsons Nocturа†; Quietude; *UK*: Noctura; *USA*: Preferred Remedies Sleep.

Patchouli

Пачули.

Profile

Patchouli (*Pogostemon cablin*, Lamiaceae) is the source of patchouli oil, which is distilled from the dried leaves and young shoots. Patchouli oil is used in aromatherapy and perfumery.

In traditional Chinese medicine the dried aerial part is known as Guang Huo Xiang.

Homoeopathy

Patchouli oil has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Thai.*: Relief Mouth Ulcer.

Patent Blue V

Acid Blue 3; Azul Patente V; CI Food Blue 5; Colour Index No. 42051; E131; Патентованный Голубой V; Патентованный Синий V.

Calcium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclohexa-2,5-dienylidene)-5-hydroxytoluene-2,4-disulphonate.

$(C_{27}H_{31}N_2O_7S_2)_2Ca$=1159.4

CAS — 3536-49-0.

UNII — 8QE473DV1Z.

NOTE. The name Patent Blue V is also used as a synonym for Sulfan Blue (CI No. 42045) (see p. 2624.1).

Pharmacopoeias. In *Fr.*

Uses and Administration

Patent blue V is given by subcutaneous injection in a dose of 1 to 10 mL of a 2.5% solution to colour the lymph vessels so that they can be injected with a contrast medium; a local anaesthetic may also be given. Patent blue V is also given by intravascular injection, in a solution prepared with sodium chloride 0.9% and lidocaine 1%, to visualise the arterial bed before giving intra-arterial chemotherapy.

Patent blue V is used as a food colour.

Malignant neoplasms of the breast. Intradermal injection of patent blue V at the site of a primary breast tumour has been used to identify the associated lymph nodes,[1] but concern has been expressed regarding possible long-term staining of the skin.[2]

1. Borgstein PJ, *et al.* Intradermal blue dye to identify sentinel lymph-node in breast cancer. *Lancet* 1997; 349: 1668–9.
2. Giuliano AE. Intradermal blue dye to identify sentinel lymph node in breast cancer. *Lancet* 1997; 350: 958.

Adverse Effects and Precautions

Hypersensitivity reactions may occur immediately or a few minutes after injection of patent blue V; on rare occasions they may be severe and include shock, dyspnoea, laryngeal spasm, and oedema. Nausea, hypotension, and tremor have been reported.

Giving a small dose to test for hypersensitivity has been suggested.

References.

1. Jaffer U, *et al.* Skin necrosis following patent blue V injection for sentinel node detection during breast cancer excision: case report. *Breast J* 2008; 14: 508–9.

Hypersensitivity. An urticarial rash occurred in a 5-year-old girl after use of tablets containing patent blue V to disclose the presence of dental plaque.[1] Severe anaphylactic reactions, including shock, have been reported.[2-6] Cross-sensitivity to sulfan blue has been reported.[7]

1. Chadwick BL, *et al.* Allergic reaction to the food dye patent blue. *Br Dent J* 1990; 168: 386–7.
2. Woltsche-Kahr L, *et al.* Anaphylactic shock following peritumoral injection of patent blue in sentinel lymph node biopsy procedure. *Eur J Surg Oncol* 2000; 26: 313–14.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Patent blue V and anaphylaxis. *Aust Adverse Drug React Bull* 2002; 21: 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0208.pdf (accessed 02/07/04)
4. Wöhrl S, *et al.* Near-fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004; 150: 1037–8.
5. Dewachter P, *et al.* Anaphylactic reaction to patent blue V after sentinel lymph node biopsy. *Acta Anaesthesiol Scand* 2006; 50: 245–7.
6. Bricou A, *et al.* Anaphylactic shock during the sentinel lymph node procedure for cervical cancer. *Gynecol Oncol* 2009; 114: 375–6.
7. Scherer K, *et al.* Anaphylaxis to isosulfan blue and cross-reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006; 96: 497–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Blueron.

Pegademase (rINN)

EC 3.5.4.4 (adenosine deaminase); PEG-ADA; Pegademasa; Pégadémase; Pegademasum; PEG-Adenosine Deaminase; Пэгадемаза.

CAS — 9026-93-1 (adenosine deaminase).

ATC — L03AX04.

ATC Vet — QL03AX04.

UNII — HW3H7D91F6 (pegademase bovine).

NOTE. Pegademase Bovine is *USAN*.

Profile

Pegademase is a conjugate of adenosine deaminase, an endogenous enzyme that converts adenosine to inosine, with a macrogol (polyethylene glycol). Pegademase bovine is used in the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase, in patients who are not suitable for bone marrow transplantation or in whom the transplantation has failed. It is given by intramuscular injection once every 7 days, in an initial dose of 10 units/kg; increments of 5 units/kg are then given weekly up to a usual weekly maintenance dose of 20 units/kg. A single dose of 30 units/kg should not be exceeded. Pegademase should be given with caution to patients with thrombocytopenia and avoided if the latter is severe.

References.
1. Lee CR, *et al.* Pegademase bovine: replacement therapy for severe combined immunodeficiency disease. *DICP Ann Pharmacother* 1991; 25: 1092–5.
2. Hershfield MS. Adenosine deaminase deficiency: clinical expression, molecular basis, and therapy. *Semin Hematol* 1998; 35: 291–8.
3. Gaspar HB, *et al.* How I treat ADA deficiency. *Blood* 2009; 114: 3524–32.
4. Booth C, Gaspar HB. Pegademase bovine (PEG-ADA) for the treatment of infants and children with severe combined immunodeficiency (SCID). *Biologics* 2009; 3: 349–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Adagen.

Pegaptanib Sodium *(BANM, USAN, rINNM)*

EYE-001; Natril Pegaptaniburn; NX-1838; Pegaptanib Octasodium; Pegaptanib sodico; Pégaptanib Sodique; Натрий Пегаптаниб.

CAS — 222716-86-1.
ATC — S01LA03.
ATC Vet — QS01LA03.
UNII — 3HP012Q0FH.

Uses and Administration

Pegaptanib is a pegylated modified oligonucleotide (aptamer) given as the sodium salt in the treatment of neovascular (wet) age-related macular degeneration. It is given by intravitreal injection into the affected eye in a dose of 300 micrograms once every 6 weeks. Stopping or withholding treatment should be considered if there has been no demonstrable benefit after 2 consecutive injections (i.e. at the 12-week visit).

Pegaptanib is also under investigation as an adjunct in the management of diabetic retinopathy.

Age-related macular degeneration. Pegaptanib is a pegylated modified oligonucleotide (aptamer) used in the treatment of age-related macular degeneration (AMD) (p. 880.2). It binds to and inhibits vascular endothelial growth factor (VEGF), which is a stimulant of angiogenesis thought to play a role in the neovascularisation and retinal changes associated with AMD. Pegaptanib is a selective antagonist of VEGF.[1,2]

Positive outcomes have been reported from two concurrent international multicentre prospective randomised controlled studies.[3] Vision loss was prevented and mean visual acuity improved in patients given 6-weekly injections of 300 micrograms, 1 mg, or 3 mg for 48 weeks compared with patients receiving sham injections. No dose-response relationship was found. In order to assess the effects of long-term therapy, patients who had been given pegaptanib in the first part of the study were then randomised at week 54 to receive either pegaptanib for a further 48 weeks or stop treatment, and patients who had been given sham injections were similarly re-randomised.[4] Results showed that patients given pegaptanib for a second year continued to derive additional benefit. A systematic review[5] of 5 randomised controlled studies found that pegaptanib was effective in reducing the risk of loss of visual acuity.

1. Siddiqui MAA, Keating GM. Pegaptanib: in exudative age-related macular degeneration. *Drugs* 2005; 65: 1571–7.
2. Chapman JA, Beckey C. Pegaptanib: a novel approach to ocular neovascularization. *Ann Pharmacother* 2006; 40: 1322–6.
3. Gragoudas ES, *et al.* Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; 351: 2805–16.
4. Chakravarthy U, *et al.* VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006; 113: 1508–21.
5. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/06/08).

Adverse Effects and Precautions

Endophthalmitis has been reported in patients given pegaptanib sodium and patients should be monitored for signs of infections for a week after the procedure. Retinal haemorrhage, retinal detachment, iatrogenic traumatic cataract, and raised intra-ocular pressure have also been reported. Immediate or delayed intravitreous haemorrhage may occur after injection. Common but less serious ocular adverse effects include eye pain, irritation, inflammation, blurred vision, visual disturbances, corneal oedema, punctate keratitis, and vitreous floaters.

Non-ocular adverse effects that have been reported include headache, rhinorrhoea, bronchitis, diarrhoea, dizziness, nausea, and urinary-tract infections.

Hypersensitivity reactions, including anaphylaxis or anaphylactoid reactions, and angioedema have been reported rarely within several hours of a dose.

Pegaptanib is contra-indicated in patients with active or suspected ocular or periocular infections.

Data from two concurrent international multicentre prospective randomised controlled studies[1] were analysed to assess the safety of pegaptanib after 2 years of treatment for neovascular (wet) age-related macular degeneration. The most common ocular adverse effects were attributed to the injection procedure and were transient and mild to moderate in intensity. Failure to follow the injection preparation protocol accounted for most cases of endophthalmitis. The incidence of adverse effects associated with systemic inhibition of vascular endothelial growth factor or severe ocular inflammation, cataract progression, or glaucoma was not higher in the pegaptanib-treated patients compared with patients receiving sham injections. Overall, the safety profile of pegaptanib was favourable in these studies.

1. D'Amico DJ, *et al.* VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006; 113: 992–1001.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Macugen; *Belg.*: Macugen; *Braz.*: Macugen†; *Canad.*: Macugen; *Cz.*: Macugen; *Denm.*: Macugen; *Fr.*: Macugen; *Ger.*: Macugen; *Gr.*: Macugen; *Hong Kong*: Macugen; *Hung.*: Macugen; *Irl.*: Macugen; *Ital.*: Macugen; *Neth.*: Macugen; *Norw.*: Macugen†; *Philipp.*: Macugen; *Pol.*: Macugen; *Port.*: Macugen; *Singapore*: Macugen; *Spain*: Macugen; *Swed.*: Macugen†; *Switz.*: Macugen; *Thai.*: Macugen†; *Turk.*: Macugen; *UK*: Macugen; *Ukr.*: Macugen (Макуген); *USA*: Macugen.

Pelargonium Sidoides

Kalwerbossie; Kapland-Pelargonie; Rabassam; South African Geranium; Пеларгониум Сидоидес.

UNII — 4FY2944729 (Pelargonium sidoides); *H6J53HEX8E* (Pelargonium sidoides root).

Pharmacopoeias. *Eur.* (see p. vii) contains pelargonium root.

Ph. Eur. 8: (Pelargonium Root). Dried, usually fragmented, underground organs of *Pelargonium sidoides* and/or *Pelargonium reniforme*. It contains a minimum of 2.0% of tannins, expressed as pyrogallol calculated with reference to the dried drug.

Uses and Administration

An extract of the roots of *Pelargonium sidoides* (Geraniaceae) is used in preparations for the relief of symptoms of the common cold and other respiratory-tract disorders. *Pelargonium reniforme* is used similarly.

Reviews.
1. Agbabiaka TB, *et al.* *Pelargonium sidoides* for acute bronchitis: a systematic review and meta-analysis. *Phytomedicine* 2008; 15: 378–85.
2. Brendler T, van Wyk BE. A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). *J Ethnopharmacol* 2008; 119: 420–33.
3. Timmer A, *et al.* Pelargonium sidoides extract for acute respiratory tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 05/02/10).

Adverse Effects

Hypersensitivity. Allergic reactions have been reported[1] with herbal preparations containing extracts of *Pelargonium sidoides* and *P. reniforme* used for respiratory-tract infections.

1. de Boer HJ, *et al.* Allergic reactions to medicines derived from Pelargonium species. *Drug Safety* 2007; 30: 677–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Kaloba; *Belg.*: Kaloban; *Braz.*: Kaloba; Umckan; *Chile*: Kaloba; *Cz.*: Kaloba; *Ger.*: Umckaloabo; *Hung.*: Kaloba; *Indon.*: Kaloba; *Malaysia*: Kaloba; *Mex.*: Umckaloabo; *Neth.*: Kaloba; Umkan; *Philipp.*: Kaloba; *Rus.*: Umckalor (Умкалор); *Singapore*: Kaloba; *Spain*: Kaloba; *Swed.*: Kaloba; *Switz.*: Kaloba; Umckaloabo; *Turk.*: Umca; *UK*: Dia-Cold; DiaPelargo; Kaloba; *Venez.*: Kaloba.

Multi-ingredient Preparations. *Ukr.*: Umckalor (Умкалор).

Penicilloyl-polylysine

Benzylpenicilloyl-polylysine; Peniciloil polilisina; PO-PLL; PPL.

CAS — 53608-77-8.

Description. Penicilloyl-polylysine is a polypeptide compound formed by the interaction of a penicillanic acid and polylysine of an average degree of polymerisation of 20 lysine residues per molecule.

Pharmacopoeias. *US* includes a concentrated form.

USP 36: (Benzylpenicilloyl Polylysine Concentrate). It has a molar concentration of benzylpenicilloyl moiety of not less than 0.0125 M and not more than 0.020 M. It contains one or more suitable buffers. It is not intended for direct administration. pH of the concentrate is between 6.5 and 8.5. Store in airtight containers.

Uses and Administration

Penicilloyl-polylysine is used to detect penicillin hypersensitivity. It is generally indicated only for adults with a history of penicillin hypersensitivity. After a preliminary scratch test it may then be given by intradermal injection. The development, usually within 5 to 15 minutes, of a wheal, erythema, and pruritus is generally judged a positive reaction. The incidence of penicillin hypersensitivity is stated to be less than 5% in patients showing a negative reaction. Penicilloyl-polylysine does not detect those liable to suffer late reactions or reactions due to minor antigen determinants; these reactions require other tests. False-positive reactions to penicilloyl-polylysine also occur.

Adverse Effects and Precautions

Severe hypersensitivity reactions have occasionally been reported after use of penicilloyl-polylysine; a scratch test is recommended before intradermal use.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Pre-Pen†.

Pharmacopoeial Preparations
USP 36: Benzylpenicilloyl Polylysine Injection.

Pentagastrin *(BAN, USAN, rINN)*

AY-6608; ICI-50123; Pentagastrilni; Pentagastrina; Pentagastrine; Pentagastrinum; Пентагастрин.

tert-Butyloxycarbonyl-[β-Ala[13]]gastrin-(13-17)-pentapeptide amide; Boc-β-Ala-Trp-Met-Asp-Phe—NH_2.

$C_{37}H_{49}N_7O_9S$=767.9
CAS — 5534-95-2.
ATC — V04CG04.
ATC Vet — QV04CG04.
UNII — EF0NX91490.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Pentagastrin). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dimethylformamide and in 5M ammonia. Protect from light.

Uses and Administration

Pentagastrin is a synthetic pentapeptide that is not active when given orally but when given parenterally has effects similar to those of natural gastrin. Since it stimulates the secretion of gastric acid, pepsin, and intrinsic factor, it is used as a diagnostic agent to test the secretory action of the stomach. It has been used to diagnose disorders associated with increased or decreased gastric acid secretion and in the evaluation of gastric acid secretion following vagotomy or gastric resection. The usual dose is 6 micrograms/kg by subcutaneous or intramuscular injection. By intravenous infusion the dose is 600 nanograms/kg per hour, in sodium chloride 0.9%.

Pentagastrin stimulates the secretion of pancreatic enzymes and thus has been used as a test for pancreatic function. It has also been tried in the diagnosis of medullary carcinoma of the thyroid.

Adverse Effects

Pentagastrin may cause gastrointestinal effects including nausea and abdominal cramps. Cardiovascular effects including flushing of the skin, tachycardia, and hypotension have occasionally been reported. There may be headache, drowsiness, dizziness, and altered sensations in the extremities. Hypersensitivity reactions are rare.

Precautions

Pentagastrin should be given with care to patients with acute peptic ulceration or with active pancreatic, hepatic, or biliary-tract disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Peptavlon†.

Pharmacopoeial Preparations
BP 2014: Pentagastrin Injection.

Black Pepper

Pepper; Pimenta; Piper; Перец Чёрный.
CAS — 8006-82-4 (black pepper oil).
UNII — KM66971LVF.

Pharmacopoeias. In *Chin.*, which describes both black and white pepper, and *US*, which also describes the powdered and powdered extract forms.

USP 36: (Black Pepper). The dried fully developed unripe fruits of *Piper nigrum*. It contains not less than 2.5% of piperine, calculated with reference to the dried drug. Protect from light and moisture.

Profile

Black pepper is the dried unripe fruit of *Piper nigrum* (Piperaceae). It is used as a culinary spice and is included in some herbal remedies.

Pepper oil, obtained from black pepper, is used in aromatherapy.

White pepper is the ripe fruit with the outer part of the pericarp removed. It too is used as a culinary spice.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cellasene Gold; *Austria*: Klosterfrau Melissengeist; *Cz.*: Klosterfrau Melisana; *Fr.*: Doluperine; Trikatu; *Hung.*: Herbadict; Klosterfrau Melisana; Munipyrin; *India*: Aglotus; Aptivate OS; Happy'tizer†; Tummy Ease†; *Philipp.*: Bo-D-Fense†; *Pol.*: Melisana Klosterfrau; *Rus.*: Maraslavin (Мараславин); Tentex (Тентекс); Travisil (Трависил); *Singapore*: Septilin; *Switz.*: Wala Elixir amer; *Ukr.*: Bon-Apetit (Бон-Аппетит); Bronchomed (Бронхомед); Maraslavin (Мараславин); Travisil (Трависил).

Homoeopathic Preparations. *Fr.*: Poconeol no 22.

Pepsin ⊗

Pepsiini; Pepsiinijauhe; Pepsin práškový; Pepsin, pulver; Pepsina; Pepsine; Pepsini Pulvis; Pepsino milteliai; Pepsinum; Pepsziń-por; Пепсин.
CAS — 9001-75-6.
ATC — A09AA03.
ATC Vet — QA09AA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Viet.* In *Jpn* as Saccharated Pepsin.

Ph. Eur. 8: (Pepsin Powder; Pepsin BP 2014). It is prepared from the gastric mucosa of pigs, cattle, or sheep. It contains gastric proteinases active in acid medium (pH 1 to 5). It has an activity of not less than 0.5 Ph. Eur. units/mg, calculated with reference to the dried substance. A hygroscopic, white or slightly yellow, crystalline or amorphous powder. Soluble in water; practically insoluble in alcohol. A solution in water may be slightly opalescent with a weak acidic reaction. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

Uses and Administration

Pepsin contains proteolytic enzymes secreted by the stomach, which control the degradation of proteins into proteoses and peptones. It hydrolyses polypeptides including those with bonds adjacent to aromatic or dicarboxylic L-amino-acid residues.

Pepsin has been given with dilute hydrochloric acid, or with substances such as glutamic acid hydrochloride, or betaine hydrochloride, as an adjunct in the treatment of gastric hypochlorhydria, or to treat deficiencies of digestive enzyme secretion. It has also been given for its supposed benefit as an ingredient of mixtures for dyspepsia and other gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Fermentol; *Pol.*: Mixtura Pepsini.

Multi-ingredient Preparations. *Arg.*: Docechol; Gastridin-E; Opoenterol; Tridigestivo Soubeiran; *Austral.*: Betaine Digestive Aid; Digestaid; Digestive Zyme†; Enzyme; *Austria*: Helo-acid; Helopanzym; Oroacid†; *Belg.*: Digestomen; *Braz.*: Digeplus; Essen; Peptopancreasi†; Primeral; *Canad.*: Digesdyn; Digest; Digestolax; Formula 17605 Diaplex; Lipozyme†; Multi-Zyme†; Pepsotol†; Proteozyme Forte; *Chile*: Flapex E; *China*: Dages (达吉); YiMei (怡美); *Ger.*: Pepzitrat†; *Hong Kong*: Bio-Tomosan†; Enzyme Co†; Uni-Paptase†; *Hung.*: Betacid; *India*: Afizyme; Aglozyme; Aglozyme; Alcezyme; Aldezyme; Altrazyme; Alzyme; Anzykair; Anzykair; Aristozyme; Arizyme; Arogyme; Asizyme; Astozyme; Atopep; Bactzyme; Biozyme; Canzyme; Cascazyme; Daffozyme; Dewzym; Digems-CT; Digeplex-T; Digeplex; Digeplex; Digitage; Dipep; Dipep; Disnizyme; Dorzy; Duozyme; E-Pep; Elfazyme; Endos; Entozyme; Entrozyme; Enzar; Enzofast; Enzytel; Estzyme; Extrazyme; Ferizyme; Fozyme; Fyzyme; Gaskit; Gastrofit; Genozyme; Genozyme; HG Zyme; Ifyzyme; Indozyme; Infazyme; Intazyme; Intazyme; Intrazyme Tonic; Intrazyme; Kairase; Kamozyme; KDZyme; Kingzyme; Lupizyme; Lyzyme; M-Zyme; Maprazyme; Martiz; NBGest; Nectozyme; Nifazyme; Novazyme Elachi; Nutrozyme; Onazyme; Optizyme; Panzyme; Unienzyme; *Indon.*: Librozym Plus†; Librozym†; *Israel*: Babyzim; *Ital.*: Gastro-Pepsin; *Mex.*: Ochozim; Zimotris; *Philipp.*: Spasmo-Canulase; *Pol.*: Citropepsin; *Port.*: Espasmo Canulase†; Modulanzime; *S.Afr.*: Sentinel Ulcer Mixture†; Spasmo-Canulase†; *Spain*: Digestomen Complex; Troforex Pepsico†; *Switz.*: Halipepsin†; Spasmo-Canulase; Stomacine; *Thal.*: Pepsitase; *Turk.*: Pepzan; *UK*: Enzyme Plus; *Ukr.*: Digestin (Дигестин); *USA*: Digepepsin; Panplex 2-Phase.

Perflubron *(USAN, rINN)* ⊗

Perflubrón; Perflubronum; Perfluorooctylbromide; PFOB; Перфлуброн.
1-Bromoheptadecafluorooctane.
C_8BrF_{17}=499.0
CAS — 423-55-2.
ATC — V08CX01.
ATC Vet — QV08CX01.
UNII — Q1D0Q7R4D9.

Pharmacopoeias. In *US*.

USP 36: (Perflubron). A clear, colourless, practically odourless liquid. Store in airtight containers. Protect from light.

Profile

Perfluorocarbons can absorb, transport, and release oxygen and carbon dioxide. Perflubron is a perfluorocarbon tried as an alternative to red blood cell preparations to improve gaseous transport, in particular oxygen supply, to the tissues. It may also be instilled directly to the lungs for use in partial liquid ventilation as an adjunct to mechanical ventilation in patients with respiratory failure.

Perflubron is being studied for use as an intravenous contrast medium in computed tomography and ultrasound. It has also been given orally to enhance delineation of the bowel during magnetic resonance imaging.

Other perfluorocarbons have also been used. A mixture of perfluamine (perfluorotripropylamine) and perflunafene (below) has been used to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Perfluorocarbons such as perflunafene and perfluorooctane (p. 2587.1) have been used in eye surgery.

Precautions. After liquid ventilation therapy perflubron is typically cleared from the lung within weeks but there have been isolated reports[1,2] of patients with residual perflubron in the lungs or other tissues years after treatment. No long-term clinical effects have been found but the bromine atom within perflubron renders perflubron radiodense and such patients may have residual radiographic opacities.[2]

1. Hagerty RD, *et al.* Radiographic detection of perflubron fluoromediastinum and fluororetroperitoneum 9 years after partial liquid ventilation. *Emerg Radiol* 2008; 15: 71–5.
2. Servaes S, Epelman M. Perflubron residua: 12 years following therapy. *Pediatr Radiol* 2009; 39: 393–5.

Uses. *BLOOD SUBSTITUTES.* References to the use of perflubron and other perfluorocarbons as oxygen carriers.

1. Garrelds JC. Fluosol: an oxygen-delivery fluid for use in percutaneous transluminal coronary angioplasty. *DICP Ann Pharmacother* 1990; 24: 1105–12.
2. Ravis WR, *et al.* Perfluorochemical erythrocyte substitutes: disposition and effects on drug distribution and elimination. *Drug Metab Rev* 1991; 23: 375–411.
3. Urbaniak SJ. Artificial blood. *BMJ* 1991; 303: 1348–50.
4. Jones JA. Red blood cell substitutes: current status. *Br J Anaesth* 1995; 74: 697–703.
5. Remy B, *et al.* Red blood cell substitutes: fluorocarbon emulsions and haemoglobin solutions. *Br Med Bull* 1999; 55: 277–98.
6. Lowe KC. Perfluorinated blood substitutes and artificial oxygen carriers. *Blood Rev* 1999; 13: 171–84.
7. Prowse CV. Alternatives to standard blood transfusion: availability and promise. *Transfus Med* 1999; 9: 287–99.
8. Matsumoto S, Kuroda Y. Perfluorocarbon for organ preservation before transplantation. *Transplantation* 2002; 74: 1804–9.
9. Jahr JS, *et al.* Blood substitutes and oxygen therapeutics: an overview and current status. *Am J Ther* 2002; 9: 437–43.
10. Kim HW, Greenburg AG. Artificial oxygen carriers as red blood cell substitutes: a selected review and current status. *Artif Organs* 2004; 28: 813–28.
11. Spahn DR, Kocian R. Artificial O2 carriers: status in 2005. *Curr Pharm Des* 2005; 11: 4099–4114.
12. Riess JG. Perfluorocarbon-based oxygen delivery. *Artif Cells Blood Substit Immobil Biotechnol* 2006; 34: 567–80.

RESPIRATORY DISTRESS SYNDROME. References to the use of perfluorocarbons, including perflubron, for partial liquid ventilation in neonatal respiratory distress syndrome (p. 1608.3) and acute respiratory distress syndrome (p. 1599.3).

1. Hirschl RB, *et al.* Liquid ventilation in adults, children, and full-term neonates. *Lancet* 1995; 346: 1201–2.
2. Leach CL, *et al.* Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 1996; 335: 761–7.
3. Hirschl RB, *et al.* Initial experience with partial liquid ventilation in adult patients with acute respiratory distress syndrome. *JAMA* 1996; 275: 383–9.
4. Wolfson MR, Shaffer TH. Liquid assisted ventilation update. *Eur J Pediatr* 1999; 158: S27–S31.
5. Davies M. Liquid ventilation. *J Paediatr Child Health* 1999; 35: 434–7.
6. Weis CM, Fox WW. Current status of liquid ventilation. *Curr Opin Pediatr* 1999; 11: 126–32.
7. Kacmarek RM. Liquid ventilation. *Respir Care Clin N Am* 2002; 8: 187–209.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 28/04/05).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Imagent GI; LiquiVent.

Perflunafene *(BAN, rINN)* ⊗

Perflunafène; Perflunafeno; Perflunafenum; Perfluorodecahydronaphthalene; Perfluorodecalin; Perfluorodekalin; Перфлунафен.
$C_{10}F_{18}$=462.1
CAS — 306-94-5.
UNII — 54A06VV62N.

Profile

Perflunafene is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of perflunafene, alone or with other perfluorocarbons, are used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment. Perflunafene and perfluamine have been used together for their oxygen-carrying properties in blood substitute preparations and to prevent myocardial ischaemia during percutaneous transluminal coronary angioplasty.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: F-Decalin; *Neth.*: Eftiar Decalin; *Turk.*: DK-Line†.

Multi-ingredient Preparations. *Ger.*: F-Decalin Plus; *Rus.*: Perftoran (Перфторан).

Perfluorohexylhexane ⊗

Перфторгексилгексан.
$C_{12}H_{13}F_{13}$=404.2

Profile

Perfluorohexylhexane is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of preparations containing perfluorohexylhexane, alone or with other perfluorocarbons, are used to provide temporary tamponade during ophthalmic procedures such as retinal re-attachment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Semifluoran F6H6†.

Multi-ingredient Preparations. *Ger.*: F-Octane Light.

Perfluorohexyloctane ⊗

Перфторгексилоктан.
$C_{14}H_{17}F_{13}$=432.3

Profile

Perfluorohexyloctane is a perfluorocarbon with similar properties to perflubron (above). Intra-ocular injections of preparations containing perfluorohexyloctane, alone or with other perfluorocarbons or dimeticone, are used to provide temporary tamponade during ophthalmic procedures such as retinal re-attachment.

References.

1. Rizzo S, *et al.* The combined use of perfluorohexyloctane (F6H8) and silicone oil as an intraocular tamponade in the treatment of severe retinal detachment. *Graefes Arch Clin Exp Ophthalmol* 2006; 244: 709–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: F6H8 Vitreous Substitute.

Multi-ingredient Preparations. *Ger.*: Densiron 68; F-Decalin Plus; F-Octane Plus.

Perfluorooctane ⊗

Octadecafluorooctane; Perfluoro-octa; Perfluoro-*n*-octane; Октадекафторооктан.
C_8F_{18}=438.1.
CAS — 307-34-6.
UNII — 6P6OZBK0QL.

Profile

Perfluorooctane is a perfluorocarbon with similar properties to perflubron (p. 2586.2). Intra-ocular injections of perfluorooctane, alone or with other perfluorocarbons, are used to provide temporary tamponade in ophthalmic procedures such as retinal re-attachment.

References.

1. Scott IU, *et al.* Outcomes of surgery for retinal detachment associated with proliferative vitreoretinopathy using perfluoro-n-octane: a multicenter study. *Am J Ophthalmol.* 2003; 136: 454–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: F-Octane; *Neth.*: Eftiar Octane; *USA*: Perfluoron.

Multi-ingredient Preparations. *Ger.*: F-Octane Light; F-Octane Plus.

Persic Oil

Melocotón, aceite de; Oleum Persicorum; Peach oil; Персиковое Масло (peach kernel oil); Абрикосовое Косточковое Масло (apricot kernel oil).
ATC Herb — HD02WB5007 (Prunus armeniaca oil); HD02WB5009 (Prunus persica oil).
UNII — 5M26W7T072.

Pharmacopoeias. *Chin.* and *Jpn* include Peach Kernel (Persicae Semen) and also Apricot Kernel (Armeniacae Semen).

Profile

Persic oil is the fixed oil expressed from the kernels of varieties of *Prunus persica* (peach) or *P. armeniaca* (apricot) (Rosaceae). It closely resembles almond oil (p. 2437.1) in its general characteristics and is used as an oily vehicle.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Audiclean.

Multi-ingredient Preparations. *Fr.*: Audiclean; Saugella allaitment anti-crevasses; Saugella douceur Polygyn; *Singapore*: Bio-Taches†; Disco.

Peru Balsam

Bals. Peruv.; Bálsamo del Perú; Balsamum Peruvianum; Baume du Pérou; Baume du San Salvador; Peru balzamas; Peruánský balzám; Perubalsam; Perui balzsm; Perunpalsami; Peruvian Balsam; Перуанский Бальзам.
CAS — 8007-00-9.
ATC Herb — HC05AW5004 (Myroxylon balsamum var. pereirae: balsam); HD03WX5012 (Myroxylon balsamum var. pereirae: balsam).
UNII — 8P5F881OCY.

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

Ph. Eur. 8: (Peru Balsam). The balsam obtained from the scorched and wounded trunk of *Myroxylon balsamum* var. *pereirae*. It contains not less than 45.0% w/w and not more than 70.0% w/w of esters, mainly benzyl benzoate and benzyl cinnamate.

A dark brown, viscous liquid which is not sticky, is non-drying, and does not form threads. It is transparent and yellowish-brown when viewed in a thin layer. Practically insoluble in water, freely soluble in dehydrated alcohol; not miscible with fatty oils except for castor oil. Protect from light.

Profile

Peru balsam has a very mild antiseptic action by virtue of its content of cinnamic and benzoic acids. Diluted with an equal part of castor oil, it has been used as an application to bedsores and chronic ulcers; it has also been used in topical preparations for the treatment of superficial skin lesions and pruritus. It is an ingredient of some rectal preparations used for the symptomatic relief of haemorrhoids (see p. 1808.1).

Peru balsam is an ingredient of some preparations used in the treatment of respiratory congestion. It is also used in aromatherapy.

Skin sensitisation has been reported.

References.

1. Pfüttner W, *et al.* Systemic contact dermatitis elicited by oral intake of balsam of Peru. *Acta Derm Venereol* 2003; 83: 294–5.
2. Avalos-Peralta P, *et al.* Sensitivity to *Myroxylon pereirae* resin (balsam of Peru). A study of 50 cases. *Contact Dermatitis* 2005; 52: 304–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Baume des Pyrenees; *Pol.*: Balsolan.

Multi-ingredient Preparations. *Arg.*: Anusol Duo S; Anusol-A; Anusol-HC; Anusol†; Novobroncol; *Austral.*: Anusol; Ayrton's Chilblain†; *Austria*: Mamellin; Pudan-Lebertran-Zinksalbe; Rombay; Vulpuran; *Belg.*: Perubore†; Rectovasol; *Braz.*: Anusol-HC; Balmex; Calminex H; Claudemor; *Fr.*: Agathol; Anaxeryl; Balsofumine; Brulex; Dermophil Indien; Dolirhume; Lelong Pommade; Oxyperol†; *Hong Kong*: Anusol; Haemoral†; *Hung.*: Pulmex Baby; Pulmex; *Indon.*: Sapona†; *Irl.*: Anugesic-HC; Anugesic-HC; Anusol-HC; Anusol; Anusol; *Israel*: Hemo; Pulmex; *Ital.*: Fomentil; *Malaysia*: Anucare; Anusol†; *NZ*: Anusol; *Pol.*: Aromagel†; Aromatol Hot Gel; Depulol; Hemorectal; Pulmex Baby; Rectosec; *Rus.*: Pulmex (Пульмекс)†; Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); *S.Afr.*: Anugesic†; Heilsalbe†; Ung Vernleigh; *Singapore*: Anusol; Anusol; *Spain*: Antigrietun; Cicatral; Grietalgen; Linitul; Vapores Pyt†; Vitamina F99 Topica†; *Switz.*: Dermophil Indien; Haemolan†; HEC†; Peru Stick; Pommade au Baume; Pulmex Baby; Pulmex; Rapura; Wala Baume nasal doux; Wala Baume nasal; *Thai.*: Anusol†; *UK*: Anugesic-HC†; Anugesic-HC; Anusol-HC, Plus HC; Anusol; Anusol; Dragon Balm; *USA*: Allanderm-T†; Anumed HC; Anumed; Balmex Baby; Boudreaux's All Natural Butt Paste; Boudreaux's Butt Paste; Dermuspray; Dr Dermi-Heal; Flanders Buttocks; Granulderm†; Granulex; GranuMed; Hemril; Mammol; Optase; Proderm; Saratoga; Vasolex; Venelex; Xenaderm.

Homoeopathic Preparations. *Austria*: Tonsan chronisch; *Canad.*: Formula MBC†; *Ger.*: Weleda Heilsalbe; *UK*: Balsamicum; Prost Cream.

Petroleum

Coal Oil; Oleum Petrae; Rock Oil; Steinöl.
UNII — 6ZAE7X688J.

Profile

Petroleum is a complex mixture consisting mainly of hydrocarbons that occurs naturally beneath the earth's surface; it is toxic by inhalation and by ingestion. It is used as a source for numerous compounds; those with pharmaceutical uses include hard paraffin (p. 2188.1), kerosene (p. 2191.1), liquid paraffin (p. 2191.2), petroleum spirit (p. 2201.2), and soft paraffin (p. 2211.3).

Homoeopathy

Petroleum, in both crude and refined forms, has been used in homoeopathic medicines under the following names: petroleum; petroleum rectificatum; oleum petrae.

Reviews of toxicity.

1. Seymour FK, Henry JA. Assessment and management of acute poisoning by petroleum products. *Hum Exp Toxicol* 2001; 20: 551–62.
2. Aguilera F, *et al.* Review on the effects of exposure to spilled oils on human health. *J Appl Toxicol* 2010; 30: 291–301.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Travellers Relief; *Austria*: Erbiode Haarvital; Frostsalbe†; Nausyn; Vertigoheel; *Canad.*: Cocculine; Eczema; Execalm†; Hylands Motion Sickness; *Cz.*: Cocculine; Vertigoheel; *Fr.*: Cocculine; Dermo-Drainol†; Dolitravel†; Euphorbium Complexe No 88; Tabacum Compose; *Ger.*: Genu-cyl L Ho-Len-Complex; Vertigoheel; *Hung.*: Cocculine; Vertigoheel; *Neth.*: Cocculine; Dermafleur; Emvita 10; Gravifem†; Travelin; Vertigoheel; *Port.*: Cocculine; *Rus.*: Cocculine (Коккулин); *S.Afr.*: Vertigoheel; *Switz.*: Cocculine; Nelsons Travella†; Vertigoheel; *UK*: Nausyn; Travella; *USA*: Vertigoheel.

Pexelizumab *(BAN, USAN, rINN)*

h5G1.1 scFv; h5G1.1 scFv (CDR); Pexélizumab; Pexelizumab; Пекселизумаб.
Immunoglobulin, anti-(human complement C5α-chain) (human-mouse monoclonal 5G1.1-SC chain).
CAS — 219685-93-5.
UNII — CHZ6OLQ3UU.

Profile

Pexelizumab is a recombinant humanised monoclonal antibody that acts as a complement blocker (p. 2485.1) by inhibiting terminal complement activation at the C5 protein. It is under investigation for treatment of patients undergoing coronary artery reperfusion and revascularisation procedures.

References.

1. Mahaffey KW, *et al.* Effect of pexelizumab on mortality in patients with acute myocardial infarction or undergoing coronary artery bypass surgery: a systematic overview. *Am Heart J* 2006; 152: 291–6.
2. Armstrong PW, *et al.* APEX AMI investigators. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2007; 297: 43–51.

Phaseolus Vulgaris

Bean; Bona; Chichiaro; Feijão; Feijoeiro; Frijol; Gartenbohne; Habichuela; Haricot Commun; Navy Bean; Owocnia Fasoli (fruit); Phaseoli Pericarpium (fruit); Poroto; Tamapapu; Trädgårdsböna.
UNII — HC262P51WU (Phaseolus vulgaris); N9D6982Q7Y (Phaseolus vulgaris immature fruit); M98C8416QO (Phaseolus vulgaris seed); G5A780J22X (Phaseolus vulgaris seed sprout).

Pharmacopoeias. In *Pol.*

Profile

The pods of the beans of *Phaseolus vulgaris* (*P. nanus*) (Fabaceae) have a weak diuretic action and are used in herbal medicines for urinary disorders. Phaseolus vulgaris is a source of phaseolamin, an inhibitor of alpha amylase, and extracts of bean pods have been promoted as aids to weight loss and adjuncts in the management of diabetes mellitus. Phaseolus vulgaris is included in herbal preparations for constipation, probably as a source of fibre.

The entire bean pods and the seeds are widely used as foodstuffs. Some varieties (especially kidney beans) contain toxic concentrations of lectins that are degraded by heat and require thorough cooking at a high temperature before consumption.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Delgadol; Forma 2.

Multi-ingredient Preparations. *Chile*: Delgadol Fibra; Delgadol Vita; *Cz.*: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; *Fr.*: Anastase; *Indon.*: F-Slim†; *Pol.*: Betasol; Diabetofort; Diabetosol; Dyspepsin; Melisana Klosterfrau; Nefrol; Urosept; *Rus.*: Arfazetin-E (Арфазетин-Э); *Ukr.*: Lipomin (Липомин); Sadifit (Садифит).

Phencyclidine Hydrochloride

(BANM, USAN, rINNM)

CI-395; CN-25253-2; Fenciclidina, hidrocloruro de; GP-121; Hidrocloruro de fenciclidina; NSC-40902; PCP; Phencyclidine, Chlorhydrate de; Phencyclidini Hydrochloridum; Фенциклидина Гидрохлорид.
1-(1-Phenylcyclohexyl)piperidine hydrochloride.
$C_{17}H_{25}N,HCl$=279.9
CAS — 77-10-1 (phencyclidine); 956-90-1 (phencyclidine hydrochloride).
UNII — V1JZQ7GDTX.

NOTE. The name PCP has also been used as a synonym for pentachlorophenol (p. 2159.2).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phencyclidine:

Ace; AD; Aliamba; Amoeba; Amoebae; Amp; Angel; Angel dust; Angel hair; Angel mist; Angel poke; Animal trank; Animal tranq; Animal tranquilizer; Aurora borealis; Bad pizza; Belladonna; Black dust; Black whack; Blotter acid; Blud madman; Blue madman; Boat; Bohd; Bush; Busy bee; Butt naked; Buzy bee; Cadillac; Cannabinol; Cat tranquilizer; Christal; Cigarrode cristal; CJ; Cliffhanger; Cliqum; Columbo; Cozmo's; Crazy coke; Crazy Eddie; Cristal; Crystal; Crystal joint; Crystal T; Crystal TAC; Cycline; Cyclona; Cyclone; Cyclones; Cystal T; D; Detroit pink; Devil's dust; Dipper; Dips; Dirge; Disembalming Fluid; DMT; Do it Jack; DOA; Drink; Drinks; Dummy dust; Dust; Dust joint; Dust of angels; Dusted parsley; Elephant; Elephant trank; Elephant tranquilizer; Embalming fluid; Energizer; Engelenspul; Erth; Fake STP; Fake THC; Fake X; Flakes; Flying saucers; Formaldehyde; Fresh; Fry; Fuel; Good; Goon; Goon crystal; Goon dust; Gorilla biscuits; Gorilla pills; Gorilla tab; Green; Green double domes; Green leaves; Green tea; Green tear; Half track; Happy sticks; HCP; H.c.p.; Heaven & Hell; Heaven and Hell; Herms; High;

Hinkley; Hog; Horse franks; Horse tracks; Horse trank; Horse tranquilizer; Ice; Ill; Illies; Illy momo; Jet fuel; Juice; K; Kaps; Kay Jay; K-blast; Killer; Killer joints; Killer weed; KJ; Koller joints; Kools; Kools sherms; Krystal; Krystal joint; Krystal joints; KW; LBJ; Leak; Leakie; Leaky; Leaky bolla; Leaky leak; Lemon 714; Lenos; Lethal weapon; Little ones; Live ones; Log; Love boat; Loveboat; Lovely; Mad dog; Mad man; Madman; Magic; Magic dust; Magic mist; Mean green; Mesk; Mint leaf; Mint weed; Mintweed; Missile; Mist; Monkey dust; Monkey gland; Monkey tranquilizer; More; New acid; New magic; Niebla; Oil; OPP; O.P.P.; Orange crystal; Ozone; P; Parsley; Paz; PCP; PCPA; Peace; PeaCe Pill; Peace pill; Peace pills; Peace weed; Peep; Peter Pan; Pig killer; Pit; Pits; Po-de-anjo; Polvo; Polvo de angel; Polvo de estralos; Polvo de estrellas; Porker; Puffy; Purple rain; Red devil; Red devils; Rocket fuel; Rocketfuel; Rupture; Scaffle; Scuffle; Serenity Tranquility Peace; Sernyl; Sernylan; Shabu; Sheets; Sherm; Sherm sticks; Sherman Hemsley; Shermans; Sherms; Skuffle; Smoking; Snorts; Soma; Space rock; Speed boat; Spores; Star dust; Stardust; Stick; STP; Sugar; Super; Super grass; Super joint; Super kools; Super weed; Supergrass; Surfer; Synthetic cocaine; Synthetic THT; T; TAC; Tac et tic; Taking a cruise; T-buzz; Tea; THC; Tic; Tic tac; Tick; Tic-tac; TicTac; Tish; Titch; Trank; Tranks; Tranq; TT 1; TT 2; TT 3; Venom; Vredestro; Wack; Water; Wave; Weed; Wet; Wet daddies; Wetdaddy; Whack; White horizon; White powder; Wobble weed; Wolf; Woolies; Wooly blunts; Worm; Yellow fever; Zombie; Zombie weed; Zoom; Zoot.

Uses and Administration

Phencyclidine is related chemically to ketamine (see p. 1905.1) and is a potent analgesic and anaesthetic. It was formerly given intravenously to produce an amnesic trance-like state, with analgesia, but severe adverse effects, especially postoperative psychoses, precluded its use. It was formerly used in veterinary medicine as an immobilising agent. Phencyclidine is widely abused in some countries for its hallucinogenic effects and has been taken orally, sniffed, injected, or smoked.

Many analogues of phencyclidine have been similarly abused and include:

- PHP (rolicyclidine; 1-(1-phenylcyclohexyl)pyrrolidine)
- PCC (1-piperidinocyclohexanecarbonitrile)
- PCE (*N*-ethyl-1-phenylcyclohexylamine)
- TCP (1-[1-(2-thienyl)cyclohexyl]piperidine)

Adverse Effects, Treatment, and Precautions

Phencyclidine can induce a psychosis clinically indistinguishable from schizophrenia. Adverse effects reported include bizarre and violent behaviour, hallucinations, euphoria, agitation, catatonic rigidity, disorientation, incoordination, nystagmus, hypersalivation, vomiting, convulsions, numbness, hypertension, tachycardia, rhabdomyolysis leading to renal failure, acidosis, and, occasionally, malignant hyperthermia. Severe intoxication may result in respiratory depression, coma, and death.

In cases of phencyclidine overdose, activated charcoal should preferably be given within 1 hour of ingestion; multiple doses may be of benefit since phencyclidine is actively secreted into the gastrointestinal tract. Treatment of the adverse effects of phencyclidine is symptomatic; if agitated the patient should be kept quiet in a darkened room, and diazepam given if necessary. Butyrophenone antipsychotics such as haloperidol have been used for severe behavioural problems and psychoses, although they are associated with adverse effects and some suggest that they should generally be avoided. Phenothiazines may lower the seizure threshold and should also be avoided. Hyperthermia should be treated. Renal excretion should be promoted by hydration and use of diuretics if necessary. Acidification of the urine is no longer recommended since acidosis may be exacerbated and renal failure precipitated.

Breast feeding. The American Academy of Pediatrics[1] has stated that, when used as a drug of abuse by a breast-feeding mother, phencyclidine has caused hallucinogenic effects in 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 02/07/04)

Phenolsulfonphthalein

Czerwień fenolowa; Fenolsulfoniftaleiini; Fenolsolfonftaleína; Fenolsulfonftalein; Fenolsulfonftaleína; Fenolsulfonftaleínas; Fenolszulfonftalein; Phenol Red; Phénolsulfonephtaléine; Phenolsulfonphthaleinum; Phenolsulphonphthalein (BAN); PSP; Фенолсульфонфталеин.

4,4′-(3*H*-2,1-Benzoxathiol-3-ylidene)diphenol *S,S*-dioxide.

$C_{19}H_{14}O_5S$=354.4

CAS — 143-74-8.
ATC — V04CH03.
ATC Vet — QV04CH03.
UNII — I6G9Y0J1OJ.

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

Ph. Eur. 8: (Phenolsulfonphthalein; Phenolsulphonphthalein BP 2014). A bright to dark red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

USNF 31: (Phenolsulfonphthalein). A bright-red to dark-red, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol.

Profile

Phenolsulfonphthalein has been used as a test of renal function by estimating the rate of urinary excretion after intravenous administration. It has also been given intramuscularly.

Alkaline urine is coloured red to violet.

Phenolsulfonphthalein has also been used as a drug ingestion indicator, a marker in drug absorption studies, and in a test of residual urine.

Hypersensitivity reactions to phenolsulfonphthalein may occasionally occur.

Phenylpropanol

Ethyl Phenyl Carbinol; Etilfenilcarbinol; Fenilpropanol; α-Hydroxypropylbenzene; SH-261; Фенилпропанол.

1-Phenylpropan-1-ol; α-Ethylbenzyl alcohol.

$C_9H_{12}O$=136.2

CAS — 93-54-9.
UNII — 0F897O3O4M.

Pharmacopoeias. In *Chin.*

Profile

Phenylpropanol is a choleretic used for the treatment of biliary-tract and gastrointestinal disorders.

Phloroglucinol *(BAN)*

Floroglucina; Floroglucinol; Floroglucynol; Floroglusinoli; Phloroglucin; Phloroglucinolum; Флороглуцинол.

Benzene-1,3,5-triol.

$C_6H_6O_3$=126.1

CAS — 108-73-6.
ATC — A03AX12.
ATC Vet — QA03AX12.
UNII — DHD7FFG6YS.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dihydrate.

Ph. Eur. 8: (Phloroglucinol, Anhydrous; Phloroglucinolum Anhydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Ph. Eur. 8: (Phloroglucinol Dihydrate; Phloroglucinolum Dihydricum). A white or almost white powder. Sparingly soluble in water; freely soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in a mixture of alcohol and water has a pH of 4.0 to 6.0. Protect from light.

Profile

Phloroglucinol is an antispasmodic that has been given orally as the hydrate in a usual dose of 160 mg at the onset of symptoms, which may be repeated if necessary. It is also given orally in a preparation with trimethylphloroglucinol in daily doses of 480 mg; lower doses have been given by intravenous or intramuscular injection, and rectally.

Uses. Short-term treatment for one week with a combination of phloroglucinol and trimethylphloroglucinol has been reported[1] to provide fast relief of acute pain in patients with irritable bowel syndrome (p. 1810.3).

1. Chassany O, *et al.* Acute exacerbation of pain in irritable bowel syndrome: efficacy of phloroglucinol/trimethylphloroglucinol— a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2007; **25**: 1115–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pasmovit; *Fr.*: Solispasm; Spasfon-Lyoc; Spasmocalm; Spassirex†; *Ital.*: Spasmex; *Mex.*: Panclasa Fem; Panclasa.

Multi-ingredient Preparations. *Arg.*: Nero; *Belg.*: Spasfon; *Fr.*: Meteoxane; Spasfon; *Gr.*: Spasfon; *Ital.*: Spasmex; *Mex.*: Klonaza; Modipas; Morelax; Panclasa; Tilmetin.

Phosgene

Carbonic Dichloride; Carbonyl Chloride; Chloroformyl Chloride; Cloruro de carbonilo; Dicloruro carbónico; Fosgen; Fosgeno; Oxicloruro de carbono.

$COCl_2$=98.92

CAS — 75-44-5.
UNII — 117K140075.

Uses

Phosgene is used in the chemical industry. It has been used as a war gas.

References.

1. Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med* 2001; **43**: 110–9.

Adverse Effects

Poisoning may occur from industrial use or from the generation of phosgene from chlorinated compounds such as dichloromethane, chloroform, or carbon tetrachloride in the presence of heat. Symptoms of poisoning, which may be delayed for up to 24 (rarely 72) hours, include burning of the eyes and throat, cough, dyspnoea, cyanosis, and pulmonary congestion and oedema. Death may result from anoxia. Exposure to 50 ppm may be rapidly fatal. Massive exposure may cause intravascular haemolysis, thrombus formation, and immediate death. Exertional dyspnoea may persist for months after exposure to high concentrations.

Treatment of Adverse Effects

After inhalation of phosgene or absorption from the skin, treatment consists of complete rest and inhalation of oxygen. The mouth, eyes, nose, and skin should be irrigated with copious amounts of water. Oral or parenteral corticosteroids have been used for bronchospasm but the role of inhaled corticosteroids is considered to be controversial. Antibacterials may reduce respiratory infections. Further treatment is symptomatic.

References.

1. Russell D, *et al.* Clinical management of casualties exposed to lung damaging agents: a critical review. *Emerg Med J* 2006; **23**: 421–4.

Phosphatidyl Choline

Fosfatidilcolina; Phosphatidylcholine; Фосфатидилхолин.

NOTE. The term phosphatidylcholine is sometimes used as a synonym for lecithin (p. 2542.2).

Profile

Phosphatidyl choline is a phospholipid and a constituent of lecithin (p. 2542.2). Phosphatidyl choline is an ingredient of preparations that have been promoted for liver disorders, peripheral vascular disorders, hyperlipidaemias, and fat emboli. Some injection preparations of phosphatidyl choline have been promoted for use in cosmetic surgery to remove subcutaneous fat deposits, but this use is not licensed in the UK.

Ulcerative colitis. Phosphatidyl choline is a component of mucus and plays a key role in mucosal defence. Since a disturbed mucosal barrier is believed to be a factor in the pathogenesis of ulcerative colitis, exogenous phosphatidyl choline has been investigated to improve the protective effects of colonic mucus. Controlled-release oral phosphatidyl choline was beneficial compared with placebo in patients with ulcerative colitis in 2 small short-term studies.[1,2]

1. Stremmel W, *et al.* Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. *Gut* 2005; **54**: 966–71.
2. Stremmel W, *et al.* Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. *Ann Intern Med* 2007; **147**: 603–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Essentiale N (易善复); *S. Afr.*: Adco-Sociale; Cruciale; *Singapore*: Hepakur; *Ukr.*: L'Esfal (Л'Есфаль); Lipin (Ліпін); *USA*: PhosChol.

Multi-ingredient Preparations. *Arg.*: Ilcx Gel Reductor†; *Canad.*: Nervrite; *Ger.*: Leferdivin†; Repithel; Silence; *Indon.*: Liposerin†; *Ital.*: Essaven; Linfonorm Cremagel; Mirtilux; Zeroac; *Malaysia*: Lesichol; NeuroPlus; *Philipp.*: Essentiale; Livolin; *Singapore*: Lesichol; Silence; *Switz.*: Silence†; Silence; *Ukr.*: Detoxil (Детоксил).

Phosphatidyl Serine

Fosfatidilserina; Phosphatidylserine; Серинфосфатид; Фосфатидилсерин.

Profile

Phosphatidyl serine is a phospholipid that has been tried in the treatment of organic psychiatric syndromes and investigated as a cognition adjuvant. Phosphatidyl serine is a constituent of lecithin (p. 2542.2).

Phosphoserine, which lacks the lipid and glycerol groups of phosphatidyl serine, has been used similarly; both (+)-L-phosphoserine (dexfosfoserine) and the racemic form (DL-phosphoserine) have been used. Phosphoserine has sometimes been used as a synonym for phosphatidyl serine.

References.
1. Pepping J. Phosphatidylserine. *Am J Health-Syst Pharm* 1999; **56**: 2038, 2043–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Bros; *Indon.*: Memoran; *UK*: Cognito.

Multi-ingredient Preparations. *Indon.*: Liposerin†; *Ital.*: Acutil Fosforo; Posfo Plus; Glutamin Fosforo; Memovit B12; Mirtilux; NeoBros 10; NeoBros C; NeoBros; *Spain*: Agudil†; Nucleserina; *Switz.*: Vitasprint B12; Vitasprint Complex†; *UK*: Neurozan.

Phosphoric Acid

Acide phosphorique; Acido Fosfórico; Ácido ortofosfórico; Acidum phosphoricum; Concentrated Phosphoric Acid; E338; Fosfato rūgštis; Fosfórico, ácido; Fosforihappo; Fosforsyra; Foszforsav; Kwas fosforowy; Kyselina fosforečná; Orthophosphoric Acid; Phosph. Acid; Phosphorsäure.

H_3PO_4=97.99

CAS — 7664-38-2.

UNII — E4GA8884NN.

Pharmacopoeias. *Eur.* (see p. vii) includes various concentrations. Also in *USNF*.

Ph. Eur. 8: (Phosphoric Acid, Concentrated; Phosphoric Acid BP 2014). It contains 84 to 90% w/w of H_3PO_4. A clear, colourless, corrosive, syrupy liquid. When stored at a low temperature it may solidify, forming a mass of colourless crystals which do not melt until the temperature reaches 28 degrees. Miscible with water and with alcohol. Store in glass containers.

Ph. Eur. 8: (Phosphoric Acid, Dilute). It contains 9.5 to 10.5% w/w H_3PO_4 and is prepared by mixing phosphoric acid 115 g with water 885 g.

USNF 31: (Phosphoric Acid). It contains 85 to 88% w/w of H_3PO_4. A colourless, odourless liquid of syrupy consistency. Miscible with water and with alcohol. Store in airtight containers.

USNF 31: (Diluted Phosphoric Acid). It contains 9.5 to 10.5% w/v H_3PO_4 and may be prepared by mixing phosphoric acid 69 mL with purified water to 1000 mL. A clear, colourless, odourless liquid. Store in airtight containers.

Uses and Administration

Phosphoric acid has industrial uses. Dilute phosphoric acid has been used well diluted in preparations intended for the management of nausea and vomiting (p. 1811.3); it has also been included in preparations for vaginal infections. Phosphoric acid is used in dentistry to etch tooth enamel.

Homoeopathy

Phosphoric acid has been used in homoeopathic medicines under the following names: Acidum phosphoricum; Phosphoricum acidum; Phosphoricum ac; Ac. phos.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Toxicity from mixing cleaning agents. For reference to the adverse effects of mixing phosphoric acid-based and hypochlorite-based cleaning agents see Sodium Hypochlorite, p. 1769.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Irontona†; Nervatona Calm; Nervatona Focus; Vitatona†; *Braz.*: Paratonico†; Vitonico; *Canad.*: Perfect Solutions 1-Minute†; *Chile*: Vigofortal†; *Fr.*: Biotone; Marinol; Phosphoneuros; Stimuplexe†; *Gr.*: Dulox; Enter-Out; Fleelaxat; Fleet Phospho-Soda; Frubiose Calcium; Kathargon; Mineralin; Odrinol; Phospho-Laxat; Phosphoclean; Trifalac; *India*: Neogadine; *Israel*: Peptical; *S.Afr.*: Emetrol; Emex; *Spain*: Oximen; *Thai.*: Quinradon-N†; *USA*: Emetrol; Formula EM; Nausatrol; Nausetrol.

Homoeopathic Preparations. *Austral.*: Hangover Relief; Nervatona Calm; Nervatona Focus; Vitatona Energy†; *Austria*: Acidum phosphoricum Med Complex; Barium Med Complex; China Med Complex; Erbiode-Starkungstropfen; Nervoheel; Phosphorus Med Complex; Selenium Med Complex; Veratrum Med Complex; *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Bioactiv E†; Comp-Drops 1 Stress†; Cutisitum†; Fatigue; Homeo-Form F†; Homeo-Form M†; Hylagene; Ikoplex 5†; Indigestion; Mental Alertness; Passiflora Complex†; Sedilor†; Ton 2 Complex†; *Chile*: Anacardio con Fosforo; Bioactiv E; Bioactiv P; *Cz.*: Vita C-R15 forte†; Vita C-R15†; *Fr.*: Abbe Chaupitre no 43†; Acidum Phosphoricum Complexe No 5; Acidum Phosphoricum Compose†; Passiflora Compose; Sativol†; *Ger.*: Entero-Gastreu S R4; Infi-China; Infinerval; Manuia; Nervo-Plantin†; Nervoregin H; Nervoregin; Presselin Nervenkomplex; Presselin Nervennahrung N†; Rufebran regeno†; Tondinel H; Tondinel; Virilis-Gastreu S R41; *Hung.*: Nervoheel; PSY-Stabil; *Neth.*: Cephalite; Cerebrum comp; Entero-Gastreu R4; Nervoheel; PSY-stabil; Sativol†; *Rus.*: Damiana-Plus (Дамиана-Плюс); *Switz.*: Nervoheel; *Ukr.*: Arsenic Comp Iov-Diabet (Арсеник Комп Иов-Диабет); *USA*: Preferred Remedies Fatigue.

Pharmacopoeial Preparations

BP 2014: Phosphate Oral Solution;

USP 36: Sodium Fluoride and Phosphoric Acid Gel.

Phosphorus

Fósforo; Fósforo amarillo; Fósforo blanco; Phosphor; Phosphore; White Phosphorus; Yellow Phosphorus; Фосфор.

P=30.973762

CAS — 7723-14-0.

UNII — 27YLU75U4W.

Handling. Phosphorus has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Stability and storage. Phosphorus is unstable in air and should be stored under water.

Uses

Elemental phosphorus is no longer used in medicine. Inorganic phosphates are given in deficiency states and bone diseases (see Uses and Administration of Sodium Phosphate, p. 1791.3). Phosphorus has been used in the manufacture of rat and cockroach poisons.

Homoeopathy

Phosphorus has been used in homoeopathic medicines under the following names: Phos.

Adverse Effects

Acute poisoning by yellow (white) phosphorus, a general protoplasmic poison, occurs in three distinct stages. The first stage represents local gastrointestinal irritation with intense thirst, pain, nausea, vomiting, and diarrhoea. The vomitus and stool may smell of garlic and are luminescent. Shock, delirium, convulsions, coma, and death may occur. In patients who survive, a second asymptomatic stage may be present lasting for up to several days or even weeks. The third stage represents systemic toxicity characterised by hepatic and renal damage, cardiovascular collapse, and CNS involvement including confusion, convulsions, and coma. Death may occur during either the first or third stages.

The fatal dose is about 1 mg/kg.

Symptoms of chronic poisoning are associated with defective tissue repair, including necrosis of the mandible ('phossy jaw').

Externally, phosphorus causes severe burns to the skin. Phosphorus is absorbed after skin contamination and systemic symptoms may occur.

Treatment of Adverse Effects

Gastric lavage may be considered after ingestion of elemental yellow (white) phosphorus, although the risks versus potential benefits must be considered in order to prevent spontaneous combustion. Activated charcoal may be used, although there is no clear evidence of benefit. Induction of emesis is contra-indicated. Potassium permanganate solution 1 in 5000 has been instilled into the stomach in an attempt to convert elemental phosphorus to an oxide, but there is no sound clinical reason to recommend this.

Further treatment is symptomatic and supportive and may include fluid and electrolyte replacement, and management of convulsions and renal and hepatic dysfunctions.

Contaminated areas on skin should be immersed in water or irrigated with copious amounts of warm water. Solutions containing copper sulfate have also been suggested for dermal irrigation to convert elemental phosphorus to copper phosphate, although concerns have been raised due to its potential to cause lethal haemolysis through inhibition of G6PD. Eyes contaminated with phosphorus should be irrigated with copious amounts of tepid water for at least 15 minutes. Exposed areas should be covered with wet dressings or compresses to prevent spontaneous combustion. It is essential that all particles of unoxidised phosphorus are removed from the skin. Lipid or oil-based topical preparations may increase the absorption of phosphorus through the skin and should not be used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Sigmaflex; *Austral.*: Nutribone; PM Kiddiecal; *Canad.*: Cal Mag Phos Plus D†; Liquid Cal-Mag plus Vitamin D and Phosphorus; T-OS; *Chile*: Chicovit Pharmaton; *Cz.*: Biomin H; *Hong Kong*: Dical-D†; *India*: Abrovit-Cal; Bio-Milk; Calcimilk; Calcizin; Calriz; Calstat; Estovon; Familykair; Glucose-D; Gynacea; Hycal; Lactocal; Milky-Rich; Milky-Rich; Milkytab; Osex Forte; Osex; Ossofez; Ossopan Alfa; *Indon.*: Calcidol; Obical; Phoscal; *Malaysia*: Obical; Shine Fememino; *Mex.*: Multi-Sanostol; *Singapore*: Lacto Calcium; Obical; *Thai.*: FB Fer†; *Ukr.*: Kalcinova (Кальциновa); Univit (Юнивит); *USA*: CalciCaps with iron; Dical†; Diostate; Pro-Cal.

Homoeopathic Preparations. *Austral.*: Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; Respatona Dry Cough & Nasal Congestion; *Austria*: Acidum phosphoricum Med Complex; Ambra Med Complex; Cepa Med Complex; China Med Complex; Galstena; Gripp Heel; Infludo; Nisylen†; Notta; Phosphor-Homaccord; Phosphorus Med Complex; Pneumodoron Nr 2; Robinia Med Complex; Tonsan akut; *Canad.*: Ateria-Heel†; Bryaconeel†; Cou Complex†; Detox L37; Diarrex; Echinacea Compositum; Endoteel†; Fatigue; Formula DE 226†; Formula FA 224†; Formula INF; Formula PC 223†; Hecocut†; Homeo-Form F†; Nareel†; Phosphor-Homaccord†; Rhinar†; Sinall Formula†; Spascupreel; *Chile*: Ikoplex No 23; *Cz.*: Galium; Gripp Heel; Hepeel; *Fr.*: Hypericum Complexe No 26; Momordica Complexe No 109†; Myosotis Complexe No 63†; Pulmo-Drainol†; Thuya Complexe No 37; *Ger.*: Agaricus comp Phosphorus; Delto-cyl Ho-Len-Complex; Feminon N; Gastro-Pasc; Gripp-Heel; Gripps; Infi-Echinacea; Infihepan; Infludo; Mucosa compositum; Nisylen; Nux Vomica N Oligoplex; Pancreas-Gastreu N; Pneumodoron 2; Roth's Rotacard; Thuja WA Oligoplex; Vertizin; Zincum Hevert N; *Hung.*: Gripp-Heel; Hepeel; Naso-Heel S; *Neth.*: Apo-Hepat; Chavita 5; Echilite; Emvita 15; Emvita 20; Emvita 6; Emvita 7; Gripp-Heel H; Infludo; Kind 0-6 Nisykind; Mucosa comp H; Neurovita; Nisyleen; Speci-chol; *Rus.*: Briacon (Бриакон); Galstena (Галстена); Influcid (Инфлюцид); Notta (Нотта); Tonsan-Akut (Тонзан-акут); *S. Afr.*: Gripp-Heel; Infludo†; Pneumodoron 2†; Sambucus Comp†; *Switz.*: Gripp-Heel; Hepeel; Infludo; *UK*: Infludo; *Ukr.*: Galstena (Галстена); Influcid (Инфлюцид); Notta (Нотта).

Pharmacopoeial Preparations

USP 36: Minerals Capsules; Minerals Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phosphorylcolamine

2-Aminoethanol Phosphate; 2-Aminoethyl Phosphate; Colamine Phosphate; Ethanolamine Phosphate; Fosfoetanolamina; Fosforylcholamine; Fosforylethanolamine; NSC-254167; Pe-104; *O*-Phosphocolamin; Phosphoethanolamin; Phosphoethanolamine; *O*-Phosphorylethanolamine; Phosphorylethanolamine.

2-Aminoethyl dihydrogen phosphate.

$C_2H_8NO_4P$=141.1

CAS — 1071-23-4.

Profile

Phosphorylcolamine, the phosphate ester of monoethanolamine, has been used as a tonic and dietary supplement. It has also been given as its calcium, magnesium, and potassium salts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Calcium-EAP; *Irl.*: Fosfor†; *UK*: Fosfor.

Multi-ingredient Preparations. *Arg.*: Stimulnerv; *Ger.*: Phosetamin†; *Spain*: Vita Menal.

Phosphothreonine

O-Phospho-L-threonine; *O*-Phosphono-L-threonine; L-Threonine *O*-phosphate; L-Threonine Dihydrogen Phosphate; Threoninium Dihydrogen Phosphate.

(*S*)-2-Amino-3-hydroxybutanoic acid 3-phosphate.

$C_4H_{10}NO_6P$=199.1
CAS — 1114-81-4 (L-phosphothreonine); 27530-80-9 (DL-phosphothreonine).

Profile

Phosphothreonine, the phosphorylated form of threonine (p. 2098.2), has been used in tonic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Tonotil-N; *Switz.*: Vitasprint Complex†.

Phyllanthus Amarus

Филлантус Обыкновенный (*Phyllanthus amarus*).
UNII — 5578I1KA35 (Phyllanthus amarus); *7OG98361LN* (Phyllanthus amarus *fruit*).

Pharmacopoeias. In *US*, which also includes the powdered form.

USP 36: (Phyllanthus Amarus). The dried aerial parts of *Phyllanthus amarus* (Euphorbiaceae). It contains not less than 0.25% of lignans, calculated as the sum of phyllanthin and hypophyllanthin on the dried basis. Protect from light and moisture.

Phyllanthus Niruri

Chanca Piedra; Shatter Stone; Филлантус Нирури.
UNII — N5N3MQO38G (Phyllanthus niruri); *K4EM2N538T* (Phyllanthus niruri *top*).

Profile

Phyllanthus is a large genus (more than 600 species) of shrubs, trees, and herbs of the family Euphorbiaceae. Two species particularly, *P. amarus* and *P. niruri*, are closely related in appearance, phytochemical contents, and history, and this has sometimes caused problems in identification, with subsequent confusion as to which one is being referred to in the setting of medicinal herb usage. The name bhumyaamalaki appears to be commonly used in India for these two species.

Phyllanthus amarus has been used in Ayurvedic medicine as a diuretic as well as in liver disorders.

Phyllanthus niruri has been used worldwide as a traditional herbal remedy for a variety of disorders including kidney stones and other urinary-tract disorders and jaundice and other hepatic disorders.

Phyllanthus emblica is discussed separately under Indian Gooseberry, p. 2532.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Divens; Stimuno.

Multi-ingredient Preparations. *Fr.*: Pilosuryl; *Hung.*: Livfit; *India*: Britesite; Hepaliv; Li-Verve; Livasa; Livasa; Livosil-R; Megacure-DS; Megacure-DS; *Indon.*: Biofos†; Dibost; Erphacea; Formuno; Glimunos; Gramuno; Hepimun Plus; Hepimun; Imudator; Imulan; Imunal Plus; Imunogard; Kidimun; Picula; Reliv†; Tribost; *Ital.*: Bionefrol; *Port.*: Biureol†; *Rus.*: Dipana (Дипана); *Ukr.*: Imunin (Иммунин)†; *Venez.*: Fludrac; Natrossil.

Physalis

Alkékenge; Alkekengi; Alquenque; Alquequenje; Amour en cage; Bladder Cherry; Blasenkirsche; Chinese Lantern; Coqueret; Ground Cherry; Judenkirsche; Lampionblume; Strawberry Tomato; Tomatillo inglés; Vejiga de perro; Winter Cherry; Песья Вишня; Физалис Обыкновенный.
UNII — M71L0X809T (Physalis alkekengi *fruiting top*).

NOTE. The name Winter Cherry has been applied to several plants including *Cardiospermum halicacabum* and *Withania somnifera* (see p. 2450.2) as well as *Physalis alkekengi*.

Pharmacopoeias. In *Chin.*

Profile

The berries of *Physalis alkekengi* (Solanaceae) are reputed to have diuretic properties.

Cape gooseberry is the edible fruit of *P. peruviana*.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Albo-Sang; *Indon.*: Hyric.

Picibanil

OK-432; Пицибанил.
CAS — 39325-01-4.
UNII — 2F42BH7X2L.

Profile

Picibanil is a lyophilised preparation of a low-virulence strain of *Streptococcus pyogenes* inactivated by heating with benzylpenicillin; it is reported to act as an immunomodulator. It has been given by injection in the treatment of malignant neoplasms.

References.

1. Luzzatto C, *et al.* Sclerosing treatment of lymphangiomas with OK-432. *Arch Dis Child* 2000; **82**: 316–18.
2. Sakamoto J, *et al.* Meta-analysis of adjuvant immunochemotherapy using OK-432 in patients with resected non-small-cell lung cancer. *J Immunother* 2001; **24**: 250–6.
3. Laranne J, *et al.* OK-432 (Picibanil) therapy for lymphangiomas in children. *Eur Arch Otorhinolaryngol* 2002; **259**: 274–8.
4. Sakamoto J, *et al.* Efficacy of adjuvant immunochemotherapy with OK-432 for patients with curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials. *J Immunother* 2002; **25**: 405–12.
5. Giguere CM, *et al.* Treatment of lymphangiomas with OK-432 (Picibanil) sclerotherapy: a prospective multi-institutional trial. *Arch Otolaryngol Head Neck Surg* 2002; **128**: 1137–44.
6. Watanabe M, *et al.* Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur. *Int J Clin Oncol* 2004; **9**: 98–106.
7. Sato Y, *et al.* A randomized controlled study of immunochemotherapy with OK-432 after curative surgery for gastric cancer. *J Immunother* 2004; 394–7.
8. Taniguchi T, *et al.* Clinical results of OK-432 injection therapy for ganglions. *J Dermatol* 2005; **32**: 262–5.
9. Kasahara K, *et al.* Randomized phase II trial of OK-432 in patients with malignant pleural effusion due to non-small cell lung cancer. *Anticancer Res* 2006; **26**: 1495–9.
10. Knipping S, *et al.* Sclerotherapy of cervical cysts with Picibanil (OK-432). *Eur Arch Otorhinolaryngol* 2007; **264**: 423–7.
11. Nygaard U, *et al.* New treatment of early fetal chylothorax. *Obstet Gynecol* 2007; **109**: 1088–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Picibanil.

Picrorhiza Kurroa

Kuru; Kutki; *Picrorhiza urrooa*; Picrolex.
UNII — ZB5K2O2999 (Picrorhiza kurroa *root*).

Profile

The dried and powdered rhizomes of *Picrorhiza kurroa* (Plantaginaceae) are used as an ingredient in herbal preparations for liver disorders and it has been tried as an adjunct to methoxsalen for the treatment of vitiligo. It has also been used in Ayurvedic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Herbadict; Livfit; Munipyrin; *Rus.*: Bonjigar (Бонджигар); Dipana (Дипана); Fitovit (Фитовит); *Singapore*: Hemoglo; *Ukr.*: Apitol (АПИТОЛ); Bonjigar (Бонджигар); Fitovit (Фитовит).

Pidotimod *(rINN)*

Pidotimodum; Пидотимод.
(R)-3-[(*S*)-5-Oxoprolyl]-4-thiazolidinecarboxylic acid.
$C_9H_{12}N_2O_4S$=244.3
CAS — 121808-62-6.
ATC — L03AX05.
ATC Vet — QL03AX05.
UNII — 78S363R681.

Profile

Pidotimod is an immunostimulant used in patients with cell-mediated immunodepression during respiratory- and urinary-tract infections. It is given orally in usual doses of 800 mg twice daily.

References.

1. Riboldi P, *et al.* Pidotimod: a reappraisal. *Int J Immunopathol Pharmacol* 2009; **22**: 255–62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: De Chang (得畅); Fuluyin (芙露饮); Li De (力德); Polimod (普利莫); Pu Le Yi (谱乐益); Wan Shi Ning (万适宁); WeiTian (唯田); *Gr.*: Polimod; *Ital.*: Axil; Onaka; Pigitil; Polimod; *Mex.*: Adimod; *Rus.*: Imunorix (Иммунорикс); *Ukr.*: Imunorix (Иммунорикс).

Pilewort

Celidonia menor; Escrofularia menor; Ficaire; Ficaria; Ranunculoides; Ficaria Verna; Lesser Celandine; Чистяк Весенний.
UNII — YO2M043F0W (Ranunculus ficaria).

Pharmacopoeias. In *Fr.*

Profile

Pilewort, the aerial parts of *Ranunculus ficaria* (Ranunculaceae), has astringent and demulcent properties and is used topically for the treatment of haemorrhoids.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Confortel; *Cz.*: Avenoc†; *Fr.* Avenoc; *UK*: Piletabs.

Homoeopathic Preparations. *Canad.*: Avenoc†; *Port.*: Avenoc†.

Pinaverium Bromide *(rINN)*

Bromuro de pinaverio; Pinaverii Bromidum; Pinaverio, bromuro de; Pinavérium, Bromure de; Pinaveriumbromid; Pinaveriumbromidi; Pinaveryum Bromür; Пинаверия Бромид.
4-(6-Bromoveratryl)-4-{2-[2-(6,6-dimethyl-2-norpinyl)ethoxy]ethyl}morpholinium bromide.
$C_{26}H_{41}Br_2NO_4$=591.4
CAS — 59995-65-2 (pinaverium); 53251-94-8 (pinaverium bromide).
ATC — A03AX04.
ATC Vet — QA03AX04.
UNII — 7SCF54H12J.

Profile

Pinaverium bromide is a calcium-channel blocker with some antimuscarinic-like effects. It is used for the relief of gastrointestinal spasm in usual doses of 50 mg orally three times daily at mealtimes, which may be increased if necessary up to a maximum of 100 mg three times daily.

Effects on the gastrointestinal tract. Two patients had heartburn and dysphagia after taking pinaverium bromide orally between meals; endoscopy revealed acute oesophageal ulceration, which healed on stopping treatment.[1] The manufacturer's recommendation to take pinaverium bromide during meals was emphasised.

1. André J-M, *et al.* Ulcères oesophagiens après prise de bromure de pinaverium. *Acta Endosc* 1980; **10**: 289–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dicetel; Nulite; *Braz.*: Dicetel; Siilil; *Canad.*: Dicetel; *Chile*: Eldicet; *China*: Dicetel (得舒特); *Cz.*: Dicetel†; *Fr.*: Dicetel; *Gr.*: Dicetel; *Hung.*: Dicetel; *India*: Eldicet; *Ital.*: Dicetel; *Mex.*: Dicetel; Distental; Diver; Lutropen; Pakab; Zerpyco; *Philipp.*: Eldicet; *Port.*: Dicetel; *Rus.*: Dicetel (Дицетел); *Spain*: Eldicet; *Switz.*: Dicetel; *Thai.*: Dicetel; *Turk.*: Dicetel; *Ukr.*: Dicetel (Дицетел); *Venez.*: Dicetel.

Multi-ingredient Preparations. *Mex.*: Alevian Duo.

Maritime Pine

Cluster Pine; Strandkiefer; Сосна Приморская.
CAS — 174882-69-0 (pycnogenol).
UNII — J27867F361 (Pinus pinaster); *50JZ5Z98QY* (Pinus pinaster *bark*); *0L1DQ35D6G* (Pinus pinaster *wood*).

Pharmacopoeias. In *USNF*.

USNF 31: (Maritime Pine). It consists of the bark of stems of *Pinus pinaster* (*Pinus maritima*) (Pinaceae). It contains not less than 8.0% and not more than 12.0% of procyanidins, calculated on the dried basis and is intended to be used in the preparation of extracts only and is not for direct human consumption. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from moisture.

Profile

The bark of the maritime pine, *Pinus pinaster* (*P. maritima*) (Pinaceae) is a source of flavonoid compounds (p. 2505.2). A mixture of procyanidins extracted from the bark is known as pycnogenol, although the term pycnogenols has also been applied to procyanidin flavonoids in general.

Preparations of such bark extracts are promoted for their antoxidant action.

Maritime pine is a source of pine needle oil (see Pine Oils, below). Pine needle oil from maritime pine (Pinus pinaster oil) is included in preparations for minor respiratory-tract disorders and in topical preparations for the relief of musculoskeletal, joint, and soft-tissue disorders. Turpentine oil (p. 2636.3) is distilled from the oleoresin.

Osteoarthritis. Extracts of maritime pine bark have been given as dietary supplements to patients with osteoarthritis; an evidence-based report[1] by the Arthritis Research Campaign in the UK considered that maritime pine was possibly effective in reducing pain and improving physical function.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_1101201015433 1.pdf (accessed 16/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Aseptobron; *Austral.*: Radiance; *Ital.*: Algorex; Flebil Plus; Flogofort; Signum; *Malaysia*: Evelle; Pynocarewhite; *Philipp.*: Gloww; Glucontrol; Pynocare 40 Actisome; *Singapore*: Evelle; Glow; Scar Esthetique; *UK*: Zinopin; *USA*: Pycnogenol Plus.

Pharmacopoeial Preparations
USP 36: Maritime Pine Extract.

Scots Pine

Pin Sylvestre; Pinus Sylvestris; Scotch pine; Сосна Обыкновенная (*Pinus sylvestris*).
ATC Herb — HM02AW5015 (Pinus sylvestris: balsam); HM02AW5017 (Pinus sylvestris: shoot tip); HR05WA5039 (Pinus sylvestris: balsam); HR05WA5041 (Pinus sylvestris: shoot tip).
UNII — VP00HZL9IC (Pinus sylvestris); M402HHT991 (Pinus sylvestris bark); B56B44M480 (Pinus sylvestris cone); 2HEM73Y19I (Pinus sylvestris flowering top); Q1RGP4UB73 (Pinus sylvestris leafy twig).

Pharmacopoeias. In *Fr.*

Profile

The sprouts of the Scots pine, *Pinus sylvestris* (Pinaceae), are used in herbal medicine for the treatment of catarrh and in topical preparations for mild muscular pain.

Scots pine is a source of Scots pine oil and pine needle oil (see Pine Oils, below).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Olioseptil Gorge-Larynx; Pectoflorine†; *Pol.*: DexaPini; Herbapini; Sirupus Pini Compositus; Sirupus Tussipini D; Sirupus Tussipini; Syrop Sosnowy Zlozony†; Syrop Sosnowy Zlozony.

Homoeopathic Preparations. *Austria*: Lymphomyosot; *Cz.*: Lymphomyosot; *Ger.*: Asthmakhell N; Lymphomyosot N; Lymphomyosot; *Hung.*: Lymphomyosot; *Neth.*: Asakell; Asthmakhell†; Lymfelite; *S.Afr.*: Lymphomyosot; *Ukr.*: Lymphomyosot (Лімфоміозот); Lymphomyosot N (Лімфоміозот Н).

Pine Oils

Сосновые Масла.
ATC Herb — HM02AW5013 (Pinus nigra: essential oil).

Pumilio Pine Oil

Dwarf Mountain Pine Oil; Dwarf Pine Needle Oil; Dwarf Pine Oil; Essence de Pin de Montagne; Latschenkiefernöl; Latschenöl; Oleum Pini Pumilionis; Olio di Mugo; Pin de montagne, huile essentielle de; Pini pumilionis aetheroleum; Pino mugo, aceite esencial de; Масло Сосны Горной.
CAS — 8016-46-4.
ATC Herb — HM02AW5012 (Pinus mugo: essential oil); HR05YA5017 (Pinus mugo: essential oil).
UNII — 6KF1RLN1CI.

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

Ph. Eur. 8: (Dwarf Pine Oil). An essential oil obtained by steam distillation of the fresh leaves and twigs of *Pinus mugo*. A suitable antoxidant may be added. Relative density 0.857 to 0.868. A clear, colourless or pale yellow liquid. Store in inert, well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Scots Pine Oil

Borovicová silice; Fir-wool Oil; Kiefernadelöl; Olejek sosny zwyczajnej; Oleum Pini Silvestris; Pin sylvestre, huile essentielle de; Pine Silvestris Oil; Pini silvestris aetheroleum; Pini Silvestris Etheroleum; Pini Sylvestris Aetheroleum; Scotch Pine Needle Oil; Scots Pine Needle Oil; Sylvestris Pine Oil; Масло Сосны Обыкновенной.
ATC Herb — HR05WA5040 (Pinus sylvestris: needle essential oil); HM02AW5016 (Pinus sylvestris: essential oil).
UNII — 5EXL5H740Y.

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

Ph. Eur. 8: (Pine Sylvestris Oil). An essential oil obtained by steam distillation of the fresh leaves and branches of *Pinus sylvestris*. A suitable antoxidant may be added. A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.855 to 0.875. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Pine oil from unspecified species of pine is included in preparations for the relief of coughs and cold symptoms and in topical preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Oils from fresh needles, tips, and boughs of *Pinus nigra*, *P. mugo* var. *pumilio*, *P. pinaster* (Maritime Pine, p. 2590.3), and *P. sylvestris* (Scots Pine, above) are all described as pine needle oil.

Pumilio pine oil is a volatile oil obtained by distillation from the fresh leaves of *Pinus mugo* var. *pumilio* (Pinaceae). It has been inhaled with steam, sometimes with other essential oils, to relieve cough and nasal congestion and has been applied externally as a rubefacient. It has also been used as a perfume.

Scots pine oil is obtained from the needles and tips of Scots pine (above). It is used for catarrh and related disorders of the respiratory tract, often with other volatile substances. It is applied externally for rheumatic disorders and is used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ukr.*: Fitesten (Фитестен).

Multi-ingredient Preparations. *Arg.*: Bayagel; Bronco Etersan; Inhalador Medex; Medex Rub; Medex Rub; Novobroncol; Pre Calent; *Austral.*: Biosal Arthritis†; Goanna Heat Cream; Goanna Oil Liniment; Goanna Salve†; Vicks Inhaler; *Austria*: Babix; Berggeist; Bronchostop†; Colda; Luuf Balsam; Nasanal; Opino; Piniment; Piniment; Piniment; *Belg.*: Inopectol†; *Braz.*: Peitoral Martel; *Canad.*: Artriben†; *Chile*: Hansaplast Descongestionante†; Mentholatum Inhalador; Menthose; *Cz.*: Mucoplant Eukalyptovy; Pinosol†; Pinosol; Thrombocid; Transpulmin†; *Fr.*: Aromasol; Bronchorectine au Citral; Febrectol†; Maghora†; Nazinette du Docteur Gilbert; Olioseptil Gorge-Larynx; Poudre du Marcheur†; Respirea†; *Ger.*: Bronchoforton Kinderbalsam†; Dolo-cyl†; Erkaltungs Bad N†; Euflux; Franzbranntwein†; Grippostad Erkaltungsbalsam mild; Klosterfrau Franzbranntwein Latschenkiefer†; Pinimenthol Erkaltungsinhalat; Pinimenthol Erkaltungssalbe; polio-elan†; Poly-elan; Tetesept Erkaltungs Bad; Tetesept Rheuma Badekonzentrat; Thrombocid; Transpulmin Kinderbalsam S†; Tumarol Kinderbalsam; Weleda Bronchialbalsam; *Gr.*: Opino; Pinimenthol; *Hong Kong*: Sloan's Liniment†; *Hung.*: Bronchovit; Hustagil Anticold Cream; Mentholatum Rub; Pasta Cool; Perskindol Classic; Pinosol; Pinosol; Rosarthron; *Indon.*: Sloan's Liniment†; *Irl.*: Karvol; *Israel*: Karvol; Ment-O-Cap†; Mentholatum Balm; *Ital.*: Abiostil; Altuss; Broncosedina; Calyptol; Narhinel Balsamico Bambini; Ozopulmin G; Ozopulmin; Pumilene Vapo; Sloan†; Vicks Inalante; *Mex.*: Balsamo Ifusa; *Mon.*: Bronchodermine; Bronchodermine; Calyptol; *Neth.*: Luuf Verkoudheidsbalsem; *NZ*: Karvol; Tixylix Chest Rub; Vicks Inhaler; *Philipp.*: Kamillosan M; *Pol.*: Analgol; Analgolan; Eukaliptiss; Herbolen D†; Herbolen†; Inhalol; Pinimentol; Pinosol†; Pulmonil; Reumatik; Reumosol; Rhin-Bac; *Port.*: Thrombocid; *Rus.*: Carmolis Fluid (Кармолис Жидкость); Eucabal S (Эвкабал С); Pinosol (Пиносол); Pinosol (Пиносол); Pinosol (Пиносол); Pinovitum (Пиновитум); Tussamag Balsam (Туссамаг Бальзам от Простуды)†; Urocholesan (Уроholесан); Urolesan (Уролесан); *S. Afr.*: Karvol†; Oleum Salviae Comp†; Respisniffers†; Woodwards Inhalant; *Singapore*: Karvol; *Spain*: Genurat; Pulmofasa; Sinus Inhalaciones; Vapores Pyt†; *Swed.*: Alpenkraft; *Switz.*: Denosol; Eucapinol; Liberol Baby N; Liberol N; Marament-N; Nasmer free; Novital; Perskindol Classic; Perskindol Classic; Perskindol Dolo; Pulmex; Ziegella†; *UK*: Dragon Balm; Karvol; Mentholatum Rub; Original Cabdrivers Expectorant; Pickles Smelling Salts; Potter's Catarrh Pastilles; Proctor's Pinelyptus; *Ukr.*: Bucabal Balsam S (Эвкабал Бальзам С); Eucalyptus Cold Balm Dr Theiss (-Эвкалиптовый Бальзам От Др Тайсс)†; Flavia (Флавия); Kofanol (Кофанол)†; Phytolysin Plus (Фитолизин Плюс); Pinosol (Пиносол)†; Pinosol (Пиносол); Pinosol (Пиносол); Pinovit (Піновіт); Rostiran (Ростиран); Urolesan (Уролесан); Vipratox (Випратокс); *Venez.*: Reugel.

Pinene

Пинен.
2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (α-pinene); 6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptane (β-pinene).
$C_{10}H_{16}$=136.2
CAS — 80-56-8 (α-pinene); 127-91-3 (β-pinene).

Profile

Pinene is a terpene constituent of turpentine oil (p. 2636.3) and many other essential oils and has been used in preparations for biliary-tract, urinary-tract, and other disorders. It exists as 2 isomers, α-pinene and β-pinene (nopinene, norpinene, terbenthene, terebenthene).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Anastim; Rowatinex; *Austria*: Rowachol; Rowatinex; *Chile*: Rowatinex; *China*: Qie Nuo (切诺); *Cz.*: Rowachol; Rowatinex; *Fr.*: Pectoderme†; *Ger.*: Rowachol; Rowatinex; *Hong Kong*: Neo-Rowachol; Neo-Rowatinex; Rowachol; Rowatinex; *Hung.*: Rowachol; Rowatinex; *Irl.*: Rowachol; Rowatinex; *Israel*: Rowachol; Rowatinex; *Malaysia*: Rowachol; Rowatinex; *Mex.*: Cholex; *Philipp.*: Rowachol; Rowatinex; *Pol.*: Rowachol; Rowatinex; Terpichol; *Rus.*: Rowatinex (Ровatинекс); *Spain*: Rowachol; Rowanefrin; *Thai.*: Rowachol; Rowatinex; *UK*: Rowachol; *Venez.*: Rowachol; Rowatinex.

Pipoxolan *(BAN, pINN)*

Pipoxolán; Pipoxolanum; Пипоксолан.
5,5-Diphenyl-2-(2-piperidinoethyl)-1,3-dioxolan-4-one.
$C_{22}H_{25}NO_3$=351.4
CAS — 23744-24-3.
UNII — 493GZJ5T6I.

Pipoxolan Hydrochloride *(BANM, USAN, pINNM)*

Hidrocloruro de pipoxolán; Pipoxolan, Chlorhydrate de; Pipoxolán, hidrocloruro de; Pipoxolani Hydrochloridum; Пипоксолана Гидрохлорид.
$C_{22}H_{25}NO_3.HCl$=387.9
CAS — 18174-58-8.
UNII — VIA6WM647S.

Profile

Pipoxolan has been used as the base and the hydrochloride as a smooth muscle relaxant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Irl.*: Migranat†.

Pirenoxine Sodium *(rINNM)*

Catalin Sodium; Natrii Pirenoxinum; Pirenoxina sódica; Pirénoxine Sodique; Pirfenoxone Sodium; Натрий Пиренoксин.
Sodium 1-hydroxy-5-oxo-5*H*-pyrido[3,2-*a*]phenoxazine-3-carboxylate.
$C_{16}H_7N_2NaO_5$=330.2
CAS — 1043-21-6 (pirenoxine); 51410-30-1 (pirenoxine sodium).
ATC Vet — QS01XA91.
UNII — 95JU7URF64.

Pharmacopoeias. *Jpn* includes Pirenoxine.

Profile

Pirenoxine sodium is used in the treatment of cataracts, usually as 0.005% eye drops.

References.

1. Inui S. *et al.* Contact dermatitis due to pirfenoxone. *Contact Dermatitis* 2004; 50: 375–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Clarvisol; *China*: Catalin (卡他灵); Kary Uni (卡林优); *Gr.*: Catalin; *Hong Kong*: Catalin; Kary Uni; *India*: Catalin; *Indon.*: Catalin; Kary Uni; *Ital.*: Clarvisan; Pirfalin; *Jpn*: Catalin; *Philipp.*: Catalin; Kary Uni; *Pol.*: Catalin; *Port.*: Clarvisan; *Singapore*: Catalin; Kary Uni; *Spain*: Clarvisan†; *Thai.*: Catalin; Kary Uni.

Pirfenidone *(USAN, rINN)*

AMR-69; F-647; Pirfenidona; Pirfénidone; Pirfenidonum; Пирфенидон.
5-Methyl-1-phenyl-2(1*H*)-pyridone.
$C_{12}H_{11}NO$=185.2
CAS — 53179-13-8.
UNII — D7NLD2JX7U.

Uses and Administration

Pirfenidone is an antifibrotic drug used for the treatment of mild to moderate idiopathic pulmonary fibrosis (see under Interstitial Lung Disease, p. 1607.1).

Pirfenidone is given orally and should be taken with food. In the EU, where a product supplying unit doses of 267 mg is licensed, treatment is begun by titration of doses over a 2-week period to the maintenance dose as follows:

- 267 mg 3 times daily for the first 7 days of treatment
- 534 mg 3 times daily for the next 7 days of treatment
- 801 mg 3 times daily thereafter, which is the maximum dose and should not be exceeded

Slightly lower doses are given in Japan, where a product supplying unit doses of 200 mg is available.

If 14 or more consecutive days of treatment are missed, pirfenidone treatment should be restarted using the 2-week titration schedule described above. If the interruption in treatment is less than 14 days, treatment can be resumed at the previous daily dose without titration.

In patients with persistent gastrointestinal adverse effects, the dose may be reduced to 267 to 534 mg 2 or 3 times daily, and then raised again to the recommended daily dose as tolerated. If necessary, treatment may be interrupted for 1 to 2 weeks to allow symptoms to resolve.

In the event of mild to moderate hypersensitivity reactions or rash, the dose may be reduced to 267 mg 3 times daily. If the rash persists for more than 7 days, pirfenidone should be stopped for 15 days and then re-escalated to the recommended daily dose.

Pirfenidone is also under investigation in other disorders such as multiple sclerosis, familial adenomatous polyposis, and neurofibromatosis type 1.

References.
1. Nicod LP. Pirfenidone in idiopathic pulmonary fibrosis. *Lancet* 1999; 354: 268–9.
2. Walker JE, Margolin SB. Pirfenidone for chronic progressive multiple sclerosis. *Multiple Sclerosis* 2001; 7: 305–12.
3. Nagai S, *et al.* Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. *Intern Med* 2002; 41: 1118–23.
4. Bowen JD, *et al.* Open-label study of pirfenidone in patients with progressive forms of multiple sclerosis. *Multiple Sclerosis* 2003; 9: 280–3.
5. Lindor NM, *et al.* Desmoid tumors in familial adenomatous polyposis: a pilot project evaluating efficacy of treatment with pirfenidone. *Am J Gastroenterol* 2003; 98: 1868–74.
6. Azuma A, *et al.* Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; 171: 1040–7.
7. Walker JE, *et al.* A double-blind, randomized, controlled study of oral pirfenidone for treatment of secondary progressive multiple sclerosis. *Multiple Sclerosis* 2005; 11: 149–58.
8. Babovic-Vuksanovic D, *et al.* Phase II trial of pirfenidone in adults with neurofibromatosis type 1. *Neurology* 2006; 67: 1860–2.
9. Shi S, *et al.* Single- and multiple-dose pharmacokinetics of pirfenidone, an antifibrotic agent, in healthy Chinese volunteers. *J Clin Pharmacol* 2007; 47: 1268–76.
10. Azuma A. Pirfenidone: antifibrotic agent for idiopathic pulmonary fibrosis. *Expert Rev Respir Med* 2010; 4: 301–10.
11. Cho ME, Kopp JB. Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. *Expert Opin Invest Drugs* 2010; 19: 275–83.
12. Noble PW, *et al.* CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–9.

Adverse Effects and Precautions

Adverse effects most commonly reported with pirfenidone include nausea, diarrhoea, dyspepsia, fatigue, rash, and photosensitivity reactions; dizziness and weight loss have also occurred. Other more serious reactions include jaundice and hepatic failure, and blood dyscrasias such as agranulocytosis, leucopenia, and neutropenia.

Raised liver transaminases have been reported in patients receiving pirfenidone and liver function tests should be carried out before starting treatment, and at monthly intervals for the first 6 months of treatment, then every 3 months thereafter. Use of pirfenidone is contra-indicated in patients with severe hepatic impairment or end-stage liver disease, and in severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease requiring dialysis. Patients should be cautioned to avoid or minimise exposure to direct sunlight, and to apply sunblock daily during treatment. Care should be taken if driving or operating machinery.

Interactions

Fluvoxamine inhibits the metabolism of pirfenidone resulting in a significant increase in pirfenidone exposure, and therefore concomitant administration of these two drugs is contra-indicated.

Tobacco smoking has been reported to increase the clearance of, and therefore reduce the exposure to, pirfenidone by 50%.

Pharmacokinetics

Pirfenidone is absorbed after oral doses; taking doses with food reduces peak plasma concentrations by about 50% but has only moderate effects on exposure, resulting in a lower incidence of adverse effects. It is metabolised primarily by the cytochrome P450 isoenzyme CYP1A2, with some contribution by CYP2C9, CYP2C19, CYP2D6 and CYP2E1. The major metabolite is 5-carboxy-pirfenidone; about 80% of a dose is excreted in urine within 24 hours, less than 1% as unchanged drug. The terminal elimination half-life after single doses is reported to be about 2.4 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Esbriet; *Ger.*: Esbriet; *Irl.*: Esbriet; *Jpn*: Pirespa; *Neth.*: Esbriet; *Norw.*: Esbriet; *Swed.*: Esbriet; *UK*: Esbriet.

Pirglutargine

Arginina, piroglutamato de; Arginine Pidolate; Arginine Pyroglutamate; Пидолат Аргинина.
L-Arginine DL-pyroglutamate.
$C_{11}H_{21}N_5O_5$=303.3
CAS — 64855-91-0.
UNII — 808T94CEU6.

Profile

Pirglutargine has been used for its reputed cerebral stimulant effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Port.*: Detoxergon.

Pirisudanol Maleate *(rINNM)*

Dimaleato de pirisuccideanol; Dimaleato de pirisudanol; Pirisudanol, dimaleato de; Pirisudanol, Maléate de; Pirisudanoli Maleas; Pyrisuccideanol Maleate; Пирисуданола Малеат.
2-Dimethylaminoethyl 5-hydroxy-4-hydroxymethyl-6-methyl-3-pyridylmethyl succinate maleate.
$C_{18}H_{24}N_2O_6.(C_4H_4O_4)_2$=572.5
CAS — 33605-94-6 (pirisudanol); 53659-00-0 (pirisudanol maleate).
ATC — N06BX08.
ATC Vet — QN06BX08.

Profile

Pirisudanol is the succinic acid ester of pyridoxine and of deanol. It has been given orally as the maleate in the management of impaired mental function in doses of up to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Nadexen; *Port.*: Pridana; *Spain*: Mentis.

Pitofenone Hydrochloride *(rINNM)*

Hidrocloruro de pitofenona; Pitofénone, Chlorhydrate de; Pitofenoni Hydrochloridum; Питофенона Гидрохлорид.
Methyl 2-[4-(2-piperidinoethoxy)benzoyl]benzoate hydrochloride.
$C_{22}H_{25}NO_4.HCl$=403.9
CAS — 54063-52-4 (pitofenone); 1248-42-6 (pitofenone hydrochloride).
UNII — HE1ZA4ZBEX.

Profile

Pitofenone hydrochloride has been used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Algifen Neo; Algifen; Analgin; Spasmopan; *Fin.*: Litalgin; *India*: Combispas; Nidi Spas; Nobel Spas; Novaspas; *Pol.*: Spasmalgon; *Rus.*: Bioralgin (Биоралгин); Bral (Брал); Bralangine (Бралангин); Maxigan (Максиган); Nebalgan (Небалган); Novigan (Новиган); Plenalgin (Пленалгин); Renalgan (Реналган); Revalgin (Ревалгин); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); *Thai.*: Donagan; Kanegan†; *Ukr.*: Baralginus (Баралгинус)†; Novigan (Новиган); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); *Venez.*: Plemibar.

Powdered Pituitary (Posterior Lobe) ⊗

Hipófisis pulverizada (neurohipófisis); Hypophysis Cerebri Pars Posterior; Hypophysis Sicca; Ipofisi Posteriore; Pituitarium Posterius Pulveratum; Pituitary; Posterior Pituitary.

NOTE. Pituitary Extract (Posterior) is *BAN*.

Pharmacopoeias. In *Chin.*

Profile

Powdered pituitary (posterior lobe) is a preparation from the posterior lobes of mammalian pituitary bodies. It has oxytocic, pressor, antidiuretic, and hyperglycaemic actions and has generally been replaced by compounds or preparations with more specific actions such as oxytocin (p. 2143.1) and desmopressin (p. 2355.1).

It has been included in preparations of combined tissue extracts promoted as tonics or for a variety of non-endocrine disorders. Hypersensitivity reactions, including anaphylaxis, have occasionally been reported.

Plantain

Llantén; Llantén mayor; Plantain grand; Подорожник большой (*Plantago major*).
ATC Herb — HC05AW5005 (Plantago major: *leaf*).
UNII — W2469WNO6U.

Pharmacopoeias. *Chin.* and *Jpn.* include the herb and seeds from *Plantago asiatica*. *Chin* also permits *P. depressa*.

Profile

The seeds and leaves of the common or greater plantain (*Plantago major*) are reported to possess diuretic and antihaemorrhagic properties. They are used in herbal preparations.

The Asian plantain (*P. asiatica*) and the depressed plantain (*P. depressa*) are also used in herbal medicine. The seeds of some other species of *Plantago* are used as the bulk laxatives ispaghula and psyllium (see p. 1849.1).

The ribwort plantain (*P. lanceolata*) is described on p. 2604.2.

Homoeopathy

Plantain has been used in homoeopathic medicine under the following names: Plantago; Plantago major; Plant. m.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Ultrabalance-Herbulk†; *Rus.*: Plantacid (Плантацид); Plantaglucid (Плантаглюцид).

Multi-ingredient Preparations. *Canad.*: Natraway Sport 1 & 2†; Natraway Sport 3†; *Chile*: Propolkit; Propolkit; *Indon.*: Hyric; Renax; *Port.*: Erpecalm; *Rus.*: Evalar (Эвалар); Fitanti (Фитантис); Kliophyt (Клиофит); Pectorales Species No 2 (Грудной Сбор 2); *Switz.*: DemoPectol; Kernosan Elixir; Pectoral N; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; *Ukr.*: Pectoral (Пектoрал); Stoptussin Fito (Стоптуссин).

Homoeopathic Preparations. *Austral.*: Earache Relief†; *Austria*: Echinacea-Cosmoplex; *Canad.*: Viburcol; *Chile*: Droseriel; Gug/X†; Llanten†; TBR/X; *Cz.*: Viburcol; *Fr.*: Abbe Chaupitre no 66†; Millefolium Complexe No 7†; *Ger.*: Entzundungstropfen; Enuroplant N; Viburcol N; *Hung.*: Viburcol; *Neth.*: Auriculite; Enulite; Homeocare keelspray; Oteel H; Ricura; Viburcol H; Vinceel H; *Port.*: Homeodent†; *Rus.*: Plantago-Plus (Плантаго-Плюс); Tabacum-Plus (Табакум-Плюс); *S.Afr.*: Viburcol; *Switz.*: Viburcol N.

Plastics

Plásticos.

Pharmacopoeias. Many pharmacopoeias include standards for plastic containers and closures.

Profile

Plastic materials have many uses in medicine and pharmacy, but may give rise to adverse effects, either by direct contact of the plastic with tissues or by indirect contact (for example, when a solution stored in a plastic container, such as a disposable syringe, is injected). Adverse

effects may also arise among workers through handling the materials or by inhaling fumes during manufacture.

Pure polymeric plastics appear to be of low toxicity, though carcinogenic effects have been produced by some on prolonged implantation. However, some monomers are toxic, as may be substances added during manufacture to impart specific physical properties. These additives include plasticisers added to reduce brittleness, ultraviolet-ray absorbers to prevent degradation by light, and antioxidants and lubricants which are sometimes needed for satisfactory processing. Monomer residues or additives can leach out from the finished plastic materials and have been the main causes of adverse effects. These may include haemolysis of blood cells, thrombosis, hypersensitivity reactions, pre-cancerous changes, and local tissue necrosis. Silicone particles have been shed from dialysis tubing resulting in hypersplenism, pancytopenia, and occasionally in the production of a granulomatous hepatitis.

See also under Vinyl Chloride, p. 2645.3, Methylmethacrylate, p. 2558.2, and Polytef, p. 2594.2.

Platinum

Plaatina; Plat; Platin; Platina; Platina; Platine; Platino; Platins; Platyna; Платина.
Pt=195.084
CAS — 7440-06-4.
UNII — 49DFR088MY.

Chloroplatinic Acid

Acide hexachloroplatinique; Acido cloroplatinico; Cloroplatínico, ácido; Heksakloroplatinahappo; Hexachloorplatinazuur; Hexachloridoplatinsäure; Hexakloro-platina(IV)-sav; Kloroplatinasyra; Kwas chloroplatynowy; Платинохлористоводородная Кислота.
Hexachloroplatinic acid hexahydrate.
$H_2PtCl_6.6H_2O$=517.9
CAS — 16941-12-1 (anhydrous chloroplatinic acid); 18497-13-7 (chloroplatinic acid hexahydrate).
UNII — Q65224GJ7F (chloroplatinic acid); 9W7LR29OOB (chloroplatinic acid hexahydrate).

NOTE. The names Platinic Chloride and Platinum Chloride have been applied to both chloroplatinic acid and platinum tetrachloride.

Platinum Tetrachloride

Platinum Chloride; Platinum (IV) Chloride; Tetrachloroplatinum.
$PtCl_4$=336.9
CAS — 13454-96-1.

Profile

Platinum is a noble metal used industrially for its catalytic properties. It is also used in jewellery, and platinum alloys have occasionally been used in dentistry. Platinum compounds such as chloroplatinic acid and platinum tetrachloride also have industrial uses. Aqueous solutions of platinum tetrachloride have been used in corneal tattooing procedures.

For the use of platinum compounds as antineoplastics, see Cisplatin, p. 766.1.

Homoeopathy

Platinum and its compounds have been used in homoeopathic medicines under the following names:

- Platinum metal: Platinum metallicum; Platina; Platin
- Chloroplatinic acid or platinum tetrachloride: Platinum muriaticum; Platinum Chloridum.

References.
1. Khan AO, Meyer D. Corneal tattooing for the treatment of debilitating glare in a child with traumatic iris loss. *Am J Ophthalmol* 2005; **139**: 920–1.

Adverse effects. Exposure to platinum compounds may result in irritation of the eyes, nose, and throat. Long-term exposure may lead to respiratory and skin sensitisation; contact allergy to platinum metal is very rare.

References.
1. Koch P, Baum HP. Contact stomatitis due to palladium and platinum in dental alloys. *Contact Dermatitis* 1996; **34**: 253–7.
2. Cristaudo A, *et al.* Occupational hypersensitivity to metal salts, including platinum, in the secondary industry. *Allergy* 2005; **60**: 159–64.
3. Fowler JF, *et al.* Positive patch-test reactions to platinum are rare. *Dermatitis* 2008; **19**: 146–7.
4. Wiseman CL, Zereini F. Airborne particulate matter, platinum group elements and human health: a review of recent evidence. *Sci Total Environ* 2009; **407**: 2493–500.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Cz.*: Lamioflur†; Platina; *Fr.*: Aurum Complexe No 38†; Ferrum Complexe No 29; *Ger.*: Bomaklim; Calmvalera; Cocculus Oligoplex; Thuja WA Oligoplex; Zincum Hevert N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Neth.*: Chavita 2; Emvita 4.

Pleurisy Root

Asclepia tuberosa; Butterfly Weed; Hierba de mariposa; Inmortal; Плевритный Корень.
UNII — 4X6S7KQ99Y (Asclepias tuberosa); Y62M9GTW4A (Asclepias tuberosa flowering top); 1ZL82U5D18 (Asclepias tuberosa root).

Profile

The root of *Asclepias tuberosa* (Asclepiadaceae) has traditionally been used for pleurisy and other respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Broncafect; *UK*: Anti-bron; Chest Mixture; Cough Soother Herbal Syrup; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover.

Homoeopathic Preparations. *Fr.*: Boripharm No 23; *Ger.*: Neuralgie-Injektopas SL.

Pokeroot

Espinaca de Indias; Fitolaca; Granilla; Hierba carmín; Hierba de la oblea; Mechoacan; Poke Root; Tintilla; Uva de América; Фитолакка Американская (*Phytolacca americana*).

Pharmacopoeias. In *Chin.*

Profile

Pokeroot, the root of *Phytolacca decandra* (*P. americana*) (Phytolaccaceae) has emetic, purgative, anti-inflammatory, and anti-infective actions. It has been used for rheumatic and arthritic disorders, and for respiratory-tract infections, but is highly toxic in large doses and is not generally recommended. It has also been used externally for skin disorders.

The related species, *P. dodecandra*, is the source of the molluscicide endod (p. 2154.2).

Homoeopathy

Pokeroot has been used in homoeopathic medicines under the following names: Phytolacca; Phytolacca americana; Phytolacca americana e baccis; Phytolacca e baccis; Phytolacca decandra; Phyto.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Echinacea Royale; *Fr.*: Homeoplasmine; *UK*: Napiers Oral Skin Soother Herbal Relief; Psorasolv.

Homoeopathic Preparations. *Austria*: Echinacea-Cosmoplex; Lymphdiaral; Vocara; *Canad.*: Angeel†; Calendula +; Calnor†; Echinacea Compositum; Echinacea L40†; Homeoplasmine; Hylands Sore Throat; Larydol†; Roxalia; Sore Throat; *Chile*: Fucus Especial; Lessfat; *Cz.*: Angin-Heel S; Homeogene 9; *Fr.*: Angipax; Boripharm No 10†; Camilia; Echinacea Complexe No 40; Homeogene 9; Phytogargarisme†; Pulviplasmine†; Scrofularia Compose; Thuya Complexe No 37; *Ger.*: Adenolin-Entoxin NN; Angina-Gastreu S R1; Bryorheum N; Entzundungstropfen; Febro-cyl L Ho-Len-Complex; G1-Injektopas; Homvioartrin; Lymphaden Complex; Lymphaden; Lymphdiaral; Lymphdiaral; Lymphozil H; Otofren; Rheuma-Pasc; Tonsipret; *Hung.*: Angin-Heel; Homeogene 9; *Neth.*: Belachin-Gastreu R1; Echinacea comp; Homeocare keelspray; Homeocare Revito; Homeocare Uro; Homeogene 9†; Lymfelite; Lymphdiaral; Mercurius-Heel; Spiroflor; Vinceel H; *Port.*: Homeogene 9; Homeoplasmine†; *Rus.*: Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Tonsipret (Тонзипрет); Vocara (Вокара); *Switz.*: Camilia; Homeogene 9; Homeoplasmine; Regenaplex Nr 28b; *Ukr.*: Tonsipret (Тонзипрет); Vocara (Вокара).

Poliglusam (*USAN, rINN*)

Chitosan; Poliglusamum; Полиглузам.
Poly-β-(1,4)-2-amino-2-deoxy-D-glucose.
CAS — 9012-76-4.

Pharmacopoeias. In *USNF.*

USNF 31: (Chitosan). An unbranched binary polysaccharide consisting of *N*-acetyl-D-glucosamine and D-glucosamine units linked in a (1→4) manner. It is obtained by partial deacetylation of chitin, which is extracted from the shells of edible shrimps and crabs suitable for human use. Its degree of deacetylation is 70.0 to 95.0%. A white or almost white powder or granules. Practically insoluble in water and in organic solvents; soluble in aqueous solutions of glycolic acid, of formic acid, of acetic acid, of hydrochloric acid, and of lactic acid. Store at a temperature below 30 degrees. Protect from light and moisture.

Poliglusam Hydrochloride (*rINN*)

Chitosan Hydrochloride; Chitosane, chlorhydrate de; Chitosan-hydrochlorid; Chitosanhydrochlorid; Chitosani Hydrochloridum; Chitozano hidrochloridas; Hidrocloruro de poliglusam; Kitosaanihydrokloridi; Kitosanhydroklorid; Kitozán-hidroklorid; Poliglusam, Chlorhydrate de; Poliglusami Hydrochloridum; Полиглузама Гидрохлорид.

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

Ph. Eur. 8: (Chitosan Hydrochloride). The chloride salt of an unbranched binary heteropolysaccharide consisting of the two units *N*-acetyl-D-glucosamine and D-glucosamine, obtained by partial deacetylation of chitin, normally leading to a degree of deacetylation of 70.0 to 95.0%. Chitin is extracted from the shells of shrimp and crab. A white or almost white fine powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Poliglusam is a polysaccharide composed of polymers of glucosamine and *N*-acetylglucosamine produced by partial deacetylation of chitin. It is manufactured commercially by chemical treatment of crustacean shells. Poliglusam is under investigation as a pharmaceutical excipient for formulations including oral dosage forms and gene carrier systems. It has been used as a dietary supplement in preparations for obesity and hypercholesterolaemia.

References.
1. Yiltalo R, *et al.* Cholesterol-lowering properties and safety of chitosan. *Arzneimittelforschung* 2002; **52**: 1–7.
2. Jull AB, *et al.* Chitosan for overweight or obesity. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 16/09/09).

Interactions. For reference to the effect of poliglusam on warfarin, see Dietary Supplements under Interactions of Warfarin, p. 1533.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Chito-Lafarmen; *Braz.*: Magrix; *Ital.*: Chitoderm; Formoline L112; *Switz.*: Formoline L112; *UK*: Bio Slim Silueta; Formoline L112.

Multi-ingredient Preparations. *Arg.*: Redualgas; XLS; *Braz.*: Control†; *Chile*: Biopiel; *India*: Chitosyl; *Indon.*: Betaslim; Combes†; Kitoles†; Naturlesterol; Vitaslim; *Singapore*: Chitosano; *Ukr.*: Bodimarin (Бодимарин); Liponorm (Липонорм).

Pollen and Pollen Extracts

Profile

Preparations containing pollen and pollen extracts from various plant sources have been used as nutritional supplements and in preparations for urological disorders. They are also used for allergen immunotherapy (p. 2435.1).

Bee pollen, which is flower pollen mixed with secretions from the honey bee, *Apis mellifera* (p. 2445.2), has also been used.

Adverse effects. In common with other products derived from bees, products containing bee pollen may cause serious adverse reactions. Many plant pollens may contribute to bee pollen, including common allergens such as ragweed pollen. For reference to hypersensitivity reactions with bee products, including bee pollen, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cernilton; Polenat; *Austria*: Grazax; Oralair; Prostaflor; *Belg.*: Oralair; *Canad.*: Oralair; Pollinex-R; *Cz.*: Grazax; Oralair; Pollinex; *Denm.*: Grazax; *Fin.*: Grazax; *Fr.*: Grazax; Prostal; Sodilen; *Ger.*: Cernilton†; Clustoid; Depiquick; Depot-Hal; Grazax; Pollinex Quattro; Purethal; Roxoid; TA Baume; TA Graser; TA Krauter top; TA MIX†; *Gr.*: Grazax; *Irl.*: Grazax; *Ital.*: Grazax; *Jpn*: Cernilton; *Malaysia*: Femal; Sanaxeen; *Neth.*: Allergopharma; Allergovit; Grazax; Oralair; Pollinex; Purethal; *Norw.*: Alutard; Grazax; *Pol.*: Allergovit; Catalet; Grazax; Perosall; Pollinex; *Port.*: Grazax; *Rus.*: Cernilton (Церниилтон); Fostal (Фосталь); *S.Afr.*: Allpyral Special Grass†; *Spain*: Grazax; Oralair; *Swed.*: Cernitol; Femal Balans; Grazax; *Switz.*: ALK; Grazax; Oralair; Polvac; Prostaflor†; Staloral; *Turk.*: Allergovit; *UK*: Grazax; Pollinex; Soluprick SQ.

Multi-ingredient Preparations. *Arg.*: Novo Prostasan; Optimina Fem; Optimina Plus; PR21; Prostafit; *China*: Prostat (舍尼通); *Fr.*: Propargile; Prostabiol; *Ger.*: Pollstimol; Sublivac; Suigen;

Hung.: Pollstimol; *Ital.*: Api Baby; Apistress; Bio-200; Biotrefon Plus; Longevital; Neoplus; Ottovis; Pollingel Ginseng; Pollingel; Ristabil; Taingel; *Mon.*: Serelys; *Philipp.*: Jamieson Total Energy; Korgivit-E†; *Rus.*: Prostopine (Простопин); *Singapore*: Femal; Vitaton; *UK*: Regina Royal Five; *Ukr.*: Apiprost (Апипрост); Energin (Энергин); Rotavit Royal (Ротавит Ройял); *USA*: PowerVites.

Homoeopathic Preparations. *Canad.*: Pollen Plus.

Poly A.poly U

Poli (A). poli (U); Polyadenylic-polyuridylic Acid; Поли(А).поли(У).
$(C_{10}H_{14}N_5O_7P)x.(C_9H_{13}N_2O_9P)x$
CAS — 24936-38-7.

Profile

Poly A.poly U is a double-stranded polyribonucleotide comprising polyadenylic and polyuridylic acids, and is believed to be an immunostimulant. It has been studied as an adjuvant in the management of operable solid tumours and in the management of hepatitis B. A complex of potassium polyriboadenylate-potassium polyribouridylate is used in the treatment of viral eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Poludan (Полудан).

Poly I.poly C

Poli (I). poli (C); Polyinosinic-polycytidylic Acid; Поли(И).поли(Ц).
$(C_{10}H_{13}N_4O_8P)x.(C_9H_{14}N_3O_8P)x$
CAS — 24939-03-5.
ATC — L03AX07.
ATC Vet — QL03AX07.

Profile

Poly I.poly C is a synthetic double-stranded polyribonucleotide complex of equimolar concentrations of polyinosinic and polycytidylic acids, described as a mismatched double-strand RNA.

Poly I.poly C and the complex of poly I.poly C stabilised with poly-L-lysine in carmellose [poly(ICLC)] have been found to induce the production of interferon and have been investigated in the treatment of malignant neoplasms and viral infections. In the form of poly I.poly C12U (p. 1009.2) it has been investigated for the treatment of AIDS, SARS, avian influenza, chronic fatigue syndrome, renal cell carcinoma, and invasive metastatic melanoma; poly(ICLC) has been investigated for the treatment of primary brain tumours.

Polyacrylamide

Acrylamide Polymer; Poliacrilamida; Poliakrylamid; Polyacrylamid; Polyakrylamid; 2-Propenamide Homopolymer; Полиакриламид.
Poly(2-propenamide).
CAS — 9003-05-8.

Profile

Polyacrylamides are polymers of acrylamide (p. 2429.2) and are available in different molecular weights and with different degrees of cross-linking. They form soft gels when hydrated and also have thickening, suspending, and flocculating properties. They are used in cosmetics, soft contact lenses, and electrophoretic gels, and also have many industrial uses. Polyacrylamide copolymers are also used.

Polyacrylamides may contain free acrylamide, a known toxin, and this has led to concerns about their safety.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *NZ*: Aquamid.

Multi-ingredient Preparations. *Singapore*: Bio-Taches Masque†; Bio-Taches†.

Polysaccharide-K

Polisacárido-K; PS-K; PSK; Полисахарид-К.

Profile

Polysaccharide-K is a beta-glucan protein complex isolated from a fungus, *Trametes versicolor* (*Coriolus versicolor*). It is claimed to have immunostimulant and antineoplastic properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Krestin; *Philipp.*: Kayken; *Singapore*: Stimmune.

Polytef *(USAN)*

Politef (pINN); Politefo; Politefum; PTFE; Политеф.
Poly(tetrafluoroethylene).
$(C_2F_4)_n$
CAS — 9002-84-0.

Profile

Polytef has many industrial applications. As 'Teflon' it is used on 'non-stick' cooking utensils.

A paste of polytef has been used for a variety of purposes including the treatment of aphonia, for replacement grafts in vascular surgery, and in the correction of some forms of urinary incontinence (p. 2349.2). The main concern with these procedures is migration of polytef particles. It has also been applied to the skin as a barrier paste with perfluoroalkylpolyether to reduce exposure to chemical warfare agents.

Adverse effects. Brain injury in a child was possibly associated with migration of polytef particles from a periureteral injection performed 1 year earlier.[1] Three cases of polytef adenopathy and one case of giant granuloma have been reported[2] in children who had previously undergone subureteral polytef injection for the treatment of vesicoureteral reflux. Teflon-associated granulomas (teflonomas) may produce false-positive diagnoses of malignancy during PET scans.[3,4]

1. Borgatti R, *et al.* Brain injury in a healthy child one year after periureteral injection of Teflon. *Pediatrics* 1996; **98**: 290–1.
2. Aragona F, *et al.* Polytetrafluoroethylene giant granuloma and adenopathy: long-term complications following subureteral polytetrafluoroethylene injection for the treatment of vesicoureteral reflux in children. *J Urol (Baltimore)* 1997; **158**: 1539–42.
3. Chadwick JL, *et al.* Teflon granuloma results in a false-positive "second primary" on 18F-2-deoxyglucose positron emission tomography in a patient with a history of nasopharyngeal cancer. *Am J Otolaryngol* 2007; **28**: 251–3.
4. Ondik MP, *et al.* Teflon laryngeal granuloma presenting as laryngeal cancer on combined positron emission tomography and computed tomography scanning. *J Laryngol Otol* 2009; **123**: 575–8.

Uses. References.

1. Polley JW, *et al.* The use of Teflon in orbital floor reconstruction following blunt facial trauma: a 20-year experience. *Plast Reconstr Surg* 1987; **79**: 39–43.
2. Puri P. Endoscopic correction of primary vesicoureteric reflux by subureteric injection of polytetrafluoroethylene. *Lancet* 1990; **335**: 1320–2.
3. Maskell R, *et al.* Correction of vesicoureteric reflux by endoscopic injection. *Lancet* 1991; **338**: 1460–1.
4. Anonymous. Use of Teflon preparations for urinary incontinence and vesicoureteral reflux. *JAMA* 1993; **269**: 2975–80.
5. Duckett JRA. The use of periurethral injectables in the treatment of genuine stress incontinence. *Br J Obstet Gynaecol* 1998; **105**: 390–6.
6. Su TH, *et al.* Injection therapy for stress incontinence in women. *Int Urogynecol J* 1999; **10**: 200–6.
7. Chaffange P, *et al.* Traitement endoscopique du réflux vésico-rénal chez l'enfant: résultats à court et à long terme des injections de polytétrafluoroéthylene (Téflon). *Prog Urol* 2001; **11**: 546–51.
8. Meschia M, *et al.* Injection therapy for the treatment of stress urinary incontinence in women. *Gynecol Obstet Invest* 2002; **54**: 67–72.
9. Huber TS, *et al.* Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. *J Vasc Surg* 2003; **38**: 1005–11.
10. Klinkert P, *et al.* Saphenous vein versus PTFE for above-knee femoropopliteal bypass: a review of the literature. *Eur J Vasc Endovasc Surg* 2004; **27**: 357–62.

Poplar Buds

Álamo, brotes de; Balm of Gilead; Balm of Gilead Buds; Brotes de chopo; Тополь (*Populus*).

NOTE. The name Balm of Gilead has also been applied to *Commiphora gileadensis*.

Pharmacopoeias. *Pol.* includes the leaves from *Populus nigra*.

Profile

The buds of various species of *Populus*, including *P. nigra*, *P. gileadensis*, and *P. tacamahacca* (*P. balsamifera*; *P. candicans*), have been used as an ingredient of herbal preparations for cough and topically for a variety of skin conditions and rheumatic disorders. Poplar buds contain salicin, volatile oil, resin, and other substances. The resin from poplar buds is one of the major sources of propolis (p. 2597.3). For the uses of the leaf and bark of other species of *Populus*, see Aspens, p. 2450.3.

Homoeopathy

Populus candicans has been used in homoeopathic medicines under the following names: Populus can.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Bronchial Cough; Mielocol†; *UK*: Balm of Gilead†.

Homoeopathic Preparations. *Hung.*: Gentos.

Poppy-seed Oil

Adormidera, aceite de semilla de; Amapola, aceite de semilla de; Huile d'Oeillette; Maw Oil; Oleum Papaveris; Oleum Papaveris Seminis; Маковое Масло.
UNII — 9G3Z76ES9J.

Profile

Poppy-seed oil is the fixed oil expressed from the ripe seeds of the opium poppy, *Papaver somniferum* (Papaveraceae). It is used as a substitute for olive oil for culinary and pharmaceutical purposes. It is also used in the preparation of Iodised Oil Fluid Injection (BP 2014). Commercial grades are used in making soaps, paints, and varnishes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Switz.*: Olbas.

Potassium Aminobenzoate

Aminobenzoate Potassium; Aminobenzoato potásico; Potassium Para-aminobenzoate; Аминобензоат Калия.
Potassium 4-aminobenzoate.
$C_7H_6KNO_2$=175.2
CAS — 138-84-1.
UNII — 41KZS5432U.

Pharmacopoeias. In *US*.

USP 36: (Aminobenzoate Potassium). A white crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 7, while a 5% solution has a pH of 8.0 to 9.0.

Uses and Administration

Potassium aminobenzoate has been used in the treatment of various disorders associated with excessive fibrosis, such as scleroderma (p. 1938.3) and Peyronie's disease, in usual oral doses of 12 g daily in 4 to 6 divided doses.

Peyronie's disease. Variable results have been reported with potassium aminobenzoate in the treatment of Peyronie's disease,[1-3] but evidence from well controlled studies is lacking. It has been suggested that a successful response is more likely if treatment is started in the acute stage.[2]

1. Gingell JC, Desai KM. Peyronie's disease. *BMJ* 1988; **298**: 1489–90.
2. Mohanty KC, Strachan RG. Peyronie's disease. *BMJ* 1989; **298**: 254.
3. Carson CC. Potassium para-aminobenzoate for the treatment of Peyronie's disease: is it effective? *Tech Urol* 1997; **3**: 135–9.

Adverse Effects and Precautions

Anorexia, nausea, fever, and rashes have been reported.

Potassium aminobenzoate should be given with caution to patients with renal impairment. Licensed product information recommends that treatment should be interrupted during periods of fasting, anorexia, or low food intake, to avoid the possible development of hypoglycaemia.

Effects on the liver. References.

1. Roy J, Carrier S. Acute hepatitis associated with treatment of Peyronie's disease with potassium para-aminobenzoate (Potaba). *J Sex Med* 2008; **5**: 2967–9.

Interactions

Potassium aminobenzoate can inactivate sulfonamides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Potaba; *Canad.*: Potaba; *Ger.*: Potaba; *Gr.*: Potaba; *UK*: Potaba; *USA*: Potaba.

Pharmacopoeial Preparations

USP 36: Aminobenzoate Potassium Capsules; Aminobenzoate Potassium for Oral Solution; Aminobenzoate Potassium Tablets.

Potassium Arsenite

Arsenious Acid, Potassium Salt; Potassium Arsonate; Potassium Metaarsenite.

$KAsO_2.HAsO_2$ (approximate)=253.9
CAS — 10124-50-2; 13464-35-2; 1332-10-1 (potassium arsenite solution).
UNII — HQE48MPP30.

Profile

Potassium arsenite is a trivalent arsenic compound (see Arsenic Trioxide, p. 2448.1). It has been used as a pesticide, although such use is banned in the UK.

Homoeopathy

Potassium arsenite and potassium arsenite solution have been used in homoeopathic medicines under the following names: Arsénite de potassium; Kali arsenicosum; Kalium arsen; Kalium arsenicosum; Kaliumarsenit; Potassium arsenite.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Berberis Cosmoplex†; *Canad.*: Alfalfa Tonic with Ginseng†; Alfalfa Tonic; Eczema; *Ger.*: Drufusan N†.

Potassium Borotartrate

Borotartrato potásico; Borotartrato sódico y potásico; Potassium Sodium Borotartrate; Soluble Cream of Tartar; Tartraborato potásico; Калия боротартрат.
CAS — 12001-68-2.

Profile

Potassium borotartrate is reported to have similar properties to those of bromides (p. 2460.3). It has been used in nervous disorders and has been used in photography as a retarder for alkaline developers. Chronic boron poisoning (see under Boric Acid, p. 2460.1) has been reported after the use of potassium borotartrate internally.

Potassium Bromate

924; Bromato potásico; Potasu bromian.
$KBrO_3$=167.0
CAS — 7758-01-2.
UNII — 04M835W6ZA.

Uses

Potassium bromate is an oxidising agent. It has no therapeutic uses but it has been widely used as the 'neutraliser' of thioglycollate hair-waving lotions. It has been used in the preparation of barley malt for beer. It has also been used as a flour-maturing agent but such use is no longer considered appropriate and is prohibited in some countries.

Food additive. Potassium bromate is a genotoxic carcinogen and should not be present in foods when consumed. Its use for the treatment of flour for bread-making is not appropriate.[1]

1. 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://whqlibdoc.who.int/trs/WHO_TRS_859.pdf (accessed 18/07/08)

Adverse Effects

Nausea, vomiting, severe abdominal pain, diarrhoea, and lethargy are common after ingestion of potassium bromate. Acute renal failure arising from tubular necrosis usually presents with oliguria or anuria within 1 to 3 days of significant ingestion, and is the most frequent cause of death. Ototoxicity may present as tinnitus or hearing loss within hours of ingestion, and can progress to sensorineural deafness in some patients. Ototoxicity and nephrotoxicity may be irreversible.

Potassium bromate poisoning can also produce hypotension, myocarditis, hepatitis, and encephalopathy characterised by agitation, delirium, convulsions, and coma. Microangiopathic anaemia has also been reported.

Potassium bromate is carcinogenic in *animals*.

Acute toxicity. Reports of bromate poisoning.

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; 7: 66–70.
2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; 114: 891–4.
3. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; 12: 204–9.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion of potassium bromate; use of a 2 to 5% solution of sodium bicarbonate has been suggested to reduce bromate absorption and prevent hydrobromic acid production. Activated charcoal has also been recommended as an adsorbent. Attention to the patient's fluid, acid–base, and electrolyte status is important, particularly in the presence of acute renal failure. An intravenous infusion of 100 to 500 mL of a 1% sodium thiosulfate solution has sometimes been given. Oxygen may be indicated. The prompt use of haemodialysis or peritoneal dialysis has been suggested.

Thiosulfate. Although the use of intravenous sodium thiosulfate is an accepted practice in the treatment of bromate poisoning, convincing evidence that it reduces bromate to bromide is lacking.[1,2] Oral sodium thiosulfate solutions have also been used but are no longer recommended because hydrogen sulfide, itself a powerful irritant and toxic agent, may be evolved in the presence of hydrochloric acid.[2]

1. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 570–2.
2. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; 12: 204–9.

Potassium Carbonate

Carbonat de potassi; Carbonate of Potash; Carbonato di potassio; E501 (potassium carbonates); Kalii Carbonas; Kālija karbonāts; Kalio karbonatas; Kalium Carbonicum; Kaliumcarbonaat; Kaliumcarbonat; Kaliumkarbonaatti; Kaliumkarbonat; Kālium-karbonāt; Pearl Ash; Potassium, carbonate de; Potasu węglan; Salt of Tartar; Uhličitan draselný; Калиев карбонат.
K_2CO_3=138.2
CAS — 584-08-7 (anhydrous potassium carbonate); 6381-79-9 (potassium carbonate sesquihydrate).
UNII — BQN1B9B9HA.

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

Ph. Eur. 8: (Potassium Carbonate). A white or almost white, hygroscopic granular powder. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Potassium Carbonate).

Profile

Potassium carbonate is an inorganic alkali. It has similar properties to potassium bicarbonate (p. 1780.3) but tends to be more caustic and irritating. It is used as an alkalinising agent and potassium source in pharmaceuticals and the food industry; it also has many industrial uses.

Homoeopathy

Potassium carbonate has been used in homoeopathic medicines under the following names: Kali Carbonicum Kaliumcarbonat Kalium Carbonicum Kali-c Kali. Carb.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Chlorvescent; *Spain*: Taponoto.

Multi-ingredient Preparations. *S.Afr.*: Helmontskruie†; Wonderkroonessens; *Switz.*: Silence†.

Homoeopathic Preparations. *Austria*: Cactus compositum; Cralonin; Globuli gegen Kopfschmerzen; Pumpan; *Canad.*: Ind Complex†; Lympatox; Menopause L122; *Fr.*: Abbe Chaupitre no 90†; Dolisedal†; Gentiana Complexe No 33†; Hepatocynesine†; Lachesis Complexe No 122; Sepia Complexe No 20; Soludor; Staphysagria Complexe No 92†; Vespa Complexe No 46†; *Ger.*: Aktivon; Conva-cyl Ho-Len-Complex; Cralonin; Hevert-Activon Kreislauftropen†; Infifer N; Pascodem; Strophanthus comp; *Neth.*: Cralonin H; Cralonin; Gynaelite; Homeocare Cyclo; Lymphomyosot; *Rus.*: Pumpan (Пумпан); *Switz.*: Cralonin; *Ukr.*: Pumpan (Пумпан).

Potassium Chlorate

Clorato potásico; Kalium Chloricum; Potassii Chloras; Potasu chloran.
$KClO_3$=122.5
CAS — 3811-04-9.
UNII — H35KS68EE7.

Handling and storage. Potassium chlorate is unstable and, in contact with organic or readily oxidisable substances such as charcoal, phosphorus, or sulfur it is liable to explode especially if heated or subjected to friction or percussion. It should not be allowed to come into contact with matches or surfaces containing phosphorus compounds. Reasonable steps should be taken before supplying potassium chlorate to ensure that it will not be used for the illicit preparation of explosives or fireworks.

Profile

Potassium chlorate has been used as an astringent, usually as a mouthwash or gargle. Concentrated solutions are irritant.

Acute poisoning from ingestion requires prompt symptomatic treatment. Symptoms include nausea, vomiting, diarrhoea, abdominal pain, haemolytic anaemia, haemorrhage, methaemoglobinaemia, hyperkalaemia, and renal failure. There may be liver damage and central effects with convulsions and coma.

Gastric lavage should be considered within 1 hour of ingestion of potassium chlorate; activated charcoal is also recommended by some. If methaemoglobinaemia is severe, patients may require exchange transfusion with whole blood. Several authorities consider that methylthioninium chloride should be given intravenously if methaemoglobinaemia is greater than 30%, although some have advised against such use for fear of converting chlorate to the more toxic hypochlorite.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Fletchers Sore Mouth Medicine; *Spain*: Edifaringen†; Faringenilo; Solurrinol.

Potassium Hydroxide

Ātzkali; Caustic Potash; E525; Hidróxido potásico; Hydroxid draselný; Kalii Hydroxidum; Kalii Hydroxydum; Kalio hidroksidas; Kalium Hydroxydatum; Kālium-hidroxid; Kalium-hydroksidi; Kaliumhydroxid; Potash Lye; Potassium Hydrate; Potassium, hydroxyde de; Potasu wodorotlenek.
KOH=56.11
CAS — 1310-58-3.
UNII — WZH3C48M4T.

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

Ph. Eur. 8: (Potassium Hydroxide). White or almost white, crystalline, hard masses, supplied as sticks, pellets, or irregularly shaped pieces; it is deliquescent in air, hygroscopic, and absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. Store in airtight, nonmetallic containers.

USNF 31: (Potassium Hydroxide). It contains not less than 85% of total alkali, calculated as KOH, including not more than 3.5% of K_2CO_3. White or practically white, fused masses, or small pellets, or flakes, or sticks, or other forms. It is hard and brittle and shows a crystalline fracture. Exposed to air, it rapidly absorbs carbon dioxide and moisture, and deliquesces. Soluble 1 in 1 of water, 1 in 3 of alcohol, and 1 in 2.5 of glycerol; very soluble in boiling alcohol. Store in airtight containers.

Uses and Administration

Potassium hydroxide is a powerful caustic that has been used to remove warts. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of potassium hydroxide and calcium hydroxide was known as Vienna paste. Potassium hydroxide is used to adjust the pH of solutions in pharmaceutical formulations.

Homoeopathy

Preparations of potassium hydroxide have been used in homoeopathy under the following names: Aetzstoff; Caustic Potash; Caust; Causticum; Causticum d'Hahnemann; Causticum, Hahnemann's; Causticum Hahnemanni; Kali Causticum; Kalium Causticum; Kalium Hydroxydatum; Kalium Hydroxidum; Hahnemann's Causticum; Potassic Hydrate; Tinctura Acris sine Kali

Adverse Effects and Treatment

As for Sodium Hydroxide, p. 2619.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Molutrex; Poxkare; *Ger.*: InfectoDell; *Spain*: Cerumenol.

Multi-ingredient Preparations. *Austria*: Leberinfusion; *China*: Piaojiamei (朴佳美); *Ital.*: Sekudrill†.

Homoeopathic Preparations. *Austral.*: Joint & Muscle Oral Spray†; *Austria*: Proagil; Rheuma; *Canad.*: Arthritic Pain; Artis-Heel†; Barijodeel†; Cou Complex†; Fibromyalgie; Homeo-Form AR†; Husteel†; Hylands Cough; Reneel†; War Complex†; *Chile*: Arnica Compuesta; *Cz.*: Husteel; *Fr.*: Abbe Chaupitre no 48†; Abbe Chaupitre no 79†; Dermo-Drainol†; Millefolium Complexe No 7†; Rhus Toxicodendron Complexe No 80; *Ger.*: Curare comp; Cysto-cyl L Ho-Len-Complex; Genu-cyl L Ho-Len-Complex; Grippe-Gastreu S R6; Hewecyst Blasen-Nieren†; Lumbago-Gastreu S R11; Rheuma-Pasc; Roth's RKT Tropfen; *Hung.*: Husteel; *Neth.*: Acidolite; Actelite; Chavita 2; Dulcar-

hus-Gastreu R11; Enulite; Grippe-Gastreu R6; Homeocare Allerlo; Husteel; Rhumeel; *Switz.*: Regenaplex Nr. 25c; Rheuma-Heel.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution; Potassium Hydroxide Solution.

Pramiverine Hydrochloride *(BANM, rINNM)*

EMD-9806 (pramiverine); Hidrocloruro de pramiverina; HSP-2986 (pramiverine); Pramiverina, hidrocloruro de; Pramivérine, Chlorhydrate de; Pramiverini Hydrochloridum; Прамиверина Гидрохлорид.
N-Isopropyl-4,4-diphenylcyclohexylamine hydrochloride.
$C_{21}H_{27}N,HCl$=329.9
CAS — 14334-40-8 (pramiverine); 14334-41-9 (pramiverine hydrochloride).

Profile

Pramiverine hydrochloride has been used as an antispasmodic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Systabon; *Venez.*: Sistalcin.

Multi-ingredient Preparations. *Venez.*: Sistalcin Compositum.

Pregnancy and Fertility Tests

Pruebas de embarazo y de fertilidad.

Profile

There are several types of kits available for simple pregnancy and fertility testing. A common method of detecting pregnancy is to use specific antibodies to measure the increase in chorionic gonadotrophin in the urine. The period of ovulation can be detected by measuring luteinising hormone excretion in similar ways.

These tests can give false results. Those carrying out the tests should be aware of this and of problems such as contaminated specimens, drug therapy, or other factors that could affect the result.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: After 10; Ahora Test; B-Quick; Biofem Test; Define; Discretest; Evanol; Evaplan; Evatest; Mater Test; Nueve Lunas; PG/53; Simple HCG; Tea Test; *Austral.*: Clearview HCG†; Discover Onestep Pregnancy Planning Kit; Discover Onestep; OvuPlan; Predictor; Pregnosis; *Braz.*: Baby Sure; Clearblue Easy; Clearblue; Detect Baby; Fertility Day; Maxtest; Predictor†; Unitest; *Canad.*: Clearblue†; Confirm†; Fact Plus†; First Response†; *Chile*: Clear Blue; *Fr.*: Babycheck-Plus†; BB Test; Clearblue test d'ovulation; Clearblue test de grossesse; Predictor†; Primastick†; Revelatest†; *Irl.*: Omega 1-step†; Testpack hCG-Urine†; Today Ovulation Test†; Uni-Gold hCG†; *Israel*: Clearblue; Predictor; Pregnosticon; *Ital.*: Clearblue; Clearplan†; Conferma 3 Plus; Confidelle Progress; Diagnosis; Gravitest; Illa; Predictor; *Jpn*: Gonavislide†; *Mex.*: Fertility Day; Inditest†; Pre-Baby; Quik-Check†; *NZ*: Clearblue; Clearplan†; Crystal Clear; Discover One Step; MDS Quick†; *Turk.*: Predictor; *UK*: Calista; Check-Mate; Clearblue; Clearview HCG; Concept; Discover; Early Bird; Fertell; First Response; Maybe Baby; Ovuquick; Predictor; Quick N Easy; Reveal; Test Pack Plus; *USA*: Advance; Answer; Clearblue Easy Ovulation; Clearblue Easy; Clearview HCG; Conceive Pregnancy; ept Stick Test; Fact Plus; First Response; Fortel; Nimbus; Pregnosis; QTest; QuickVue; RapidVue; TestPack Plus hCG-Urine; UCG-Slide; Unistep hCG.

Prenylamine *(BAN, USAN, rINN)* ⊗

B-436; Hoechst-12512; Prenilamina; Prenylamin; Prénylamine; Prenylaminum; Prenyyliamiini; Пренилamин.
2-Benzhydrylethyl(α-methylphenethyl)amine.
$C_{24}H_{27}N$=329.5
CAS — 390-64-7.
ATC — C01DX02.
ATC Vet — QC01DX02.
UNII — K2OH82Z000.

Prenylamine Lactate *(BANM, rINNM)* ⊗

Lactato de prenilamina; Prenilamina, lactato de; Prénylamine, Lactate de; Prenylamini Lactas; Prenylaminil Lactas; Пренилamина Лактат.
$C_{24}H_{27}N,C_3H_6O_3$=419.6
CAS — 69-43-2.
ATC — C01DX02.
ATC Vet — QC01DX02.
UNII — 6J3J6SXI7V.

Profile

Prenylamine depletes myocardial catecholamine stores and has some calcium-channel blocking activity. It was formerly used in the treatment of angina pectoris but has been superseded by less toxic drugs. Use of prenylamine has been associated with the development of ventricular arrhythmias and ECG abnormalities. Tremor and extrapyramidal symptoms have also occurred.

Primula Root

Gullviverot; Kankalingyökér; Kevätesikonjuuri; Primavera; Primavera de jardines; Primelwurzel; Primevère, racine de; Prímula; Primulae radix; Prvosenkový kořen; Racine de Primevère; Raktažolių šaknys; Schlüsselblumenwurzel; Примула (*Primula*); Первоцвет (*Primula*).
ATC Herb — HR05WA5047 (Primula veris: *rhizome*); *HR05WA5046* (Primula veris: *flower*).
UNII — W6LFQ57E4M (Primula veris); *TA94NTR55X* (Primula veris *root*).

Pharmacopoeias. *Eur.* (see p. vii) includes Primula root.

Ph. Eur. 8: (Primula Root: Primulae Radix). Consists of the whole or cut, dried rhizome and root of *Primula veris* [cowslip] or *P. elatior*[oxlip].

Profile

Primula root has expectorant properties and is used for cough and other respiratory-tract disorders.

Cowslip, the flowers, leaves, and roots of *Primula veris* (*P. officinalis*) (Primulaceae), is widely used in herbal medicine. The flowers have sedative properties and are used for insomnia, hyperactivity, and anxiety disorders. The flowers and leaves have also been used similarly to primula root.

Oxlip flowers and root (*P. elatior*) and primrose root (*P. vulgaris*) have also been used.

Homoeopathy

Cowslip has been used in homoeopathic medicines under the following names: Primula veris; Primula ver.

Primula vulgaris has been used in homoeopathic medicines under the following names: Primula vulg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Keptan.

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel; *Austral.*: Sinupret; Throat-Clear; *Austria*: Bronchithym†; Cardiodoron; Heumann's Bronchialtee; Sinupret; Solvopret†; *Canad.*: Honey Herb Cough Drops†; Original Herb Cough Drops†; *Cz.*: Biotussil; Bronchipret Tymian a Prvosenka; Sinupret; *Ger.*: Bronchicum Elixir; Bronchicum; Bronchipret; Brust- und Hustentee†; Cardiodoron; Cimicifuga comp; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N†; Equisil N†; Expectysat N; Heumann Bronchialtee Solubifix T; Kneipp Husten- und Bronchial-Tee†; Phytobronchin; Sinuforton†; Sinupret; *Hong Kong*: Sinupret; *Hung.*: Bronchicum; Bronchicum; Bronchipret; Sinupret; *Indon.*: Bronchipret†; Silex; Sinupret†; *Malaysia*: Sinupret; *Mex.*: Bisolsinus; *Neth.*: Bronchicum; *Philipp.*: Bronchipret†; Sinupret; *Pol.*: Bronchicum Eliksir†; Bronchosol; Herbapect; Sinupret; *Rus.*: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Bronchicum TP (Бронхикум ТП); Bronchipret TP (Бронхипрет ТП); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Sinupret (Синупрет); *S.Afr.*: Cardiodoron†; *Singapore*: Sinupret; *Swed.*: Sinova; *Switz.*: Bronchipret TP; Cardiodoron; DemoPectol; Kernosan Elixir; Pectoral N; Sinupret; Sirop pectoral contre la toux S; Sirop pectoral; Siropectan; Strath Gouttes contre la toux; Tisane pectorale pour les enfants; *Thai.*: Sinupret†; Solvopret TP†; *UK*: Bio-Strath Willow Formula; Onopordon Comp B; Sinueeze; Sinuherb; Spotner; *Ukr.*: Bronchipret TP (Бронхипрет ТП); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Pectoral (Пекторал); Sinupret (Синупрет).

Homoeopathic Preparations. *Canad.*: Formula C Doron†; Formula C Doroon†; *Ger.*: Biodolor; Cordiodoron†; Crataegus comp; Pflugerplex Gelsemium; Roth's RKT Tropfen; Schwoneural N.

Proadifen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de proadifeno; NSC-39690; Proadifène, Chlorhydrate de; Proadifeni Hydrochloridum; Proadifeno, hidrocloruro de; Propyladiphenine Hydrochloride; RP-5171; SKF-525A; SKF-525-A; Проадифена Гидрохлорид.
2-Diethylaminoethyl 2,2-diphenylvalerate hydrochloride.
$C_{23}H_{31}NO_2,HCl$=390.0
CAS — 302-33-0 (proadifen); 62-68-0 (proadifen hydrochloride).
UNII — 30624AA6X2.

Profile

Proadifen is a cytochrome P450 inhibitor used in the study of drug metabolism.

Probiotics

Probiotics are defined as live micro-organisms used as dietary supplements to improve the health of the host when given in adequate amounts.

Composition and viability. Some preparations of probiotics have been found to contain smaller quantities or different species of organisms to those specified on the label.[1] An FAO/WHO working group[2] published some guidelines that should be followed in order to claim that a food has a probiotic effect. These include the genus, species, and strain of the organisms in the preparation to be stated on the product label using currently recognised systematic nomenclature, and a statement of the minimum number of viable organisms remaining at the end of the product shelf-life.

1. Hamilton-Miller JMT, *et al.* "Probiotic" remedies are not what they seem. *BMJ* 1996; 312: 55–6.
2. FAO/WHO. *Guidelines for the evaluation of probiotics in food.* London Ontario, Canada: Food and Agriculture Organization of the United Nations, 2002. Also available at: http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed 11/02/08)

Lactic-acid-producing Organisms

Láctico, organismos productores de ácido; МолочноКислые Бактерии.
ATC Vet — QA07FA01.

Uses and Administration

Lactic-acid-producing organisms were first introduced as potential therapeutic agents with the idea of acidifying the intestinal contents and thus preventing the growth of putrefactive organisms. *Lactobacillus bulgaricus* (*Lactobacillus delbrueckii* subsp. *bulgaricus*), which occurs in naturally soured milk, was the organism originally used but it can be difficult to obtain growth of this organism in the intestines. Natural yogurt (p. 2649.3) is a common source of lactic-acid-producing organisms.

It is now thought that the gastrointestinal tract may play a wider part in host defences and consequently there is increasing interest in the use of live non-pathogenic microbial cultures to optimise the enteric microbiota, including in neonates. These are referred to as probiotics and are generally commensal lactic-acid producing bacteria, although some yeasts are also used. Organisms currently being used in probiotic preparations include *Lactobacillus* spp. and *Bifidobacterium* spp. Other organisms that may be used are *Enterococcus* and *Streptococcus* spp., and the yeast *Saccharomyces boulardii*.

Probiotics are promoted to restore or maintain a healthy microbial flora, and are widely available as yogurts or other fermented milk products, as well as oral dosage forms such as tablets, capsules, and powders. They are being investigated in the management of several gastrointestinal disorders including diarrhoea and inflammatory bowel disorders. Probiotics are also being investigated in vaginal disorders and allergic disorders such as atopic eczema.

A vaccine produced from strains of lactobacillus found in women with trichomoniasis has been used in the prophylaxis of recurrent trichomoniasis (see p. 2422.2).

Allergic disorders. Oral ingestion of probiotic bacteria may play a role in the development of the adaptive immune system[1] and there has been some interest in their use in the management of allergic disorders such as atopic eczema.[2-5] Early reviews[6,7] of studies in allergic disorders concluded that although there appeared to be a reasonable theoretical basis for expecting benefit with probiotics, there were insufficient data to support their inclusion in routine treatment regimens for atopic eczema, perennial allergic rhinitis, or asthma. Subsequently a systematic review[8] has concluded that probiotics are not an effective treatment for eczema and carry a small risk of adverse events such as infections and bowel ischaemia.

1. Rinne M, *et al.* Effect of probiotics and breastfeeding on the *Bifidobacterium* and *Lactobacillus/Enterococcus* microbiota and humoral immune responses. *J Pediatr* 2005; 147: 186–91.
2. Kalliomäki M, *et al.* Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; 361: 1869–71.
3. Rosenfeldt V, *et al.* Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; 145: 612–16.
4. Weston S, *et al.* Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; 90: 892–7.

5. Pölster-Holst R, *et al.* Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; 155: 1256–61.
6. Anonymous. Probiotics for atopic diseases. *Drug Ther Bull* 2005; 43: 6–8.
7. Prescott SL, Björkstén B. Probiotics for the prevention or treatment of allergic diseases. *J Allergy Clin Immunol* 2007; 120: 255–62.
8. Boyle RJ, *et al.* Probiotics for treating eczema. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 10/08/10).

Gastrointestinal disorders. Oral probiotics are under investigation for several gastrointestinal disorders and although they appear to be of benefit in some conditions, further study is required to confirm these findings. It is probable that efficacy depends on the species and strain of the organism as well as on the condition being treated.[1,2]

Conclusions from a systematic review[3] suggest that probiotics might be a useful adjunct to oral rehydration therapy in the treatment of acute infectious *diarrhoea* in adults and children. A meta-analysis[4] of studies of *Lactobacillus* therapy in children reached a similar conclusion. However, it was not possible to draw up definitive treatment guidelines because of a lack of standardisation in probiotic regimens, patient groups, or definition of acute diarrhoea between the available studies.[3,4] Meta-analyses[5,6] and a systematic review[7] of studies investigating the use of probiotics in the prevention of antibiotic-associated diarrhoea in adults[5] and children[5-7] also suggest a beneficial effect, although again, further clinical confirmation is required before they can be routinely recommended.[5-7] A review[8] of studies that looked specifically at treatment or prevention of *Clostridium difficile*-associated diarrhoea with the probiotics *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* concluded that while these specific probiotics might be useful in patients at risk of recurrent *C. difficile* infection, the potential risks of bacteraemia or fungaemia in this particular patient group might outweigh any benefit.

Probiotics have been investigated to correct aberrant intestinal microflora associated with chronic *inflammatory bowel disease* and reviews of such studies suggest some benefit in the prevention and treatment of ulcerative colitis[9-11] and maintenance of remission in pouchitis,[10-12] although the data are not so clear for Crohn's disease.[10,13,14] Larger controlled clinical studies, again with standardised probiotic preparations and treatment regimens, are necessary to establish the place of probiotics in the management of inflammatory bowel disease.[9-13] A systematic review[15] concluded that although *Bifidobacterium infantis* appeared to be effective for the management of symptoms of *irritable bowel syndrome* there were inadequate data to comment on the efficacy of other probiotics. For reference to the use of probiotics in *pancreatitis*, see p. 2580.2.

Probiotics given to preterm neonates of very low birthweight reduced the incidence and severity of *necrotising enterocolitis* in 2 randomised controlled studies.[16,17] Systematic reviews[18,19] of these and other controlled studies reached the same conclusion, although the authors called for confirmation of these results by a larger study to strengthen the case for routine use of probiotics in preterm neonates. Similar results were obtained in a later multicentre prospective randomised controlled study[20] involving a total of 434 infants of gestational age less than 34 weeks and birth-weight less than 1500 g who were given probiotics enterally for 6 weeks, although it was difficult to interpret results for infants weighing less than 750 g due to an imbalance of infants in this lower weight range between the study and control groups.

Probiotics have also been tried in constipation[21] and infantile colic.[22]

1. Anonymous. Probiotics for gastrointestinal disorders. *Drug Ther Bull* 2004; 42: 85–8.
2. Limdi JK, *et al.* Do probiotics have a therapeutic role in gastroenterology? *World J Gastroenterol* 2006; 12: 5447–57.
3. Allen SJ, *et al.* Probiotics for treating infectious diarrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 11/02/08).
4. Van Niel CW, *et al.* *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; 109: 678–84.
5. D'Souza AL, *et al.* Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; 324: 1361–6.
6. Szajewska H, *et al.* Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *J Pediatr* 2006; 149: 367–72.
7. Johnston BC, *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 11/02/08).
8. Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. *Ann Pharmacother* 2007; 41: 1212–21.
9. Bai A-P, Ouyang Q. Probiotics and inflammatory bowel diseases. *Postgrad Med J* 2006; 82: 376–82.
10. Bwaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 2006; 12: 5941–50.
11. Chapman TM, *et al.* VSL#3 probiotic mixture: a review of its use in chronic inflammatory bowel diseases. *Drugs* 2006; 66: 1371–87.
12. Holubar SD, *et al.* Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 16/08/10).
13. Rolfe VE, *et al.* Probiotics for maintenance of remission in Crohn's disease. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 11/02/08).
14. Butterworth AD, *et al.* Probiotics for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 19/03/10).
15. Brenner DM, *et al.* The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol* 2009; 104: 1033–49.
16. Bin-Nun A, *et al.* Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; 147: 192–6.
17. Lin H-C, *et al.* Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; 115: 1–4.
18. Deshpande G, *et al.* Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. *Lancet* 2007; 369: 1614–20.
19. Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/10).
20. Lin H-C, *et al.* Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. *Pediatrics* 2008; 122: 693–700.
21. Banaszkiewicz A, Szajewska H. Ineffectiveness of *Lactobacillus* GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. *J Pediatr* 2005; 146: 364–9.
22. Savino F, *et al.* *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007; 119: e124–e30. Available at: http://pediatrics.aappublications.org/cgi/reprint/119/1/e124.pdf (accessed 11/02/08)

Urogenital infections. Probiotic preparations given orally or intravaginally are under investigation for the prevention or treatment of vaginal infections. Reviews of studies in vulvovaginal candidiasis[1] and bacterial vaginosis[2] concluded that while there was some indication of benefit, larger controlled studies are required to confirm efficacy and the place of probiotics in therapy. Systematic reviews[3,4] have also found some evidence of benefit for the use of lactobacillus probiotics in the treatment of bacterial vaginosis, but did not find sufficient evidence that these probiotics were more effective than antibacterials or enhanced their efficacy.[4] Another systematic review[5] confirmed that probiotics may be of benefit in the prevention and treatment of bacterial vaginosis in pregnancy but due to insufficient data it was not possible to assess the effect that this might have in preventing preterm labour. A review[6] of studies investigating probiotics for the prevention of urinary-tract infections in women has suggested some benefit.

1. Falagas ME, *et al.* Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. *J Antimicrob Chemother* 2006; 58: 266–72.
2. Falagas ME, *et al.* Probiotics for the treatment of women with bacterial vaginosis. *Clin Microbiol Infect* 2007; 13: 657–64.
3. Oduyebo OO, *et al.* The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 24/02/10).
4. Senok AC, *et al.* Probiotics for the treatment of bacterial vaginosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 24/02/10).
5. Othman M, *et al.* Probiotics for preventing preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 11/02/08).
6. Falagas ME, *et al.* Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs* 2006; 66: 1253–61.

Adverse effects

Metabolic acidosis has occurred after use of tablets containing *Lactobacillus acidophilus*.[1] Cases of infection associated with the use of lactic-acid-producing organisms seem to be very rare,[2] although fungaemia associated with the use of *Saccharomyces boulardii*,[3] and sepsis associated with *Lactobacillus* spp.[4] have been reported. Reviews[5,6] on the safety of probiotics concluded that their overall safety record is good. However, the authors recommend caution in certain patient groups such as the elderly and premature or immunocompromised neonates because of occasional reports of sepsis that have rarely occurred in previously healthy patients.[5] Use of enterococci and streptococci as probiotics give a theoretical cause for concern since these genera include pathogenic bacteria.[5] Properties of probiotics are specific to species and strain and therefore reports on safety for one probiotic cannot be generalised to others.[5]

1. Oh MS, *et al.* D-Lactic acidosis in a man with short-bowel syndrome. *N Engl J Med* 1979; 301: 249–52.
2. Borriello SP, *et al.* Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis* 2003; 36: 775–80.
3. Piarroux R, *et al.* Are live saccharomyces yeasts harmful to patients? *Lancet* 1999; 353: 1851–2.
4. Land MH, *et al.* Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005; 115: 178–81.
5. Boyle RJ, *et al.* Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006; 83: 1256–64.
6. Hammerman C, *et al.* Safety of probiotics: comparison of two popular strains. *BMJ* 2006; 333: 1006–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acidofilofago; Flevic; Floratil; Lactinex; Tropivag; ***Austral.***: Bioglan Acidophilus†; Digestive Bio Balance; Forbiotic†; ProTract; Superdophilus†; ***Austria***: Antibiophilus; Bioflorin; Doderlein; Reflor; Symbioflor Enterococcus; Yomogi; ***Belg.***: Enterol; Lacteol; ***Braz.***: Flomicin; Floratil; Floren; Florent; Lactipan; Leiba; Repoflor; ***Canad.***: Align; Bacid; BioGaia; Florastor; Lacidofil; TuZen; ***Chile***: Bio-Flora; BioGaia; Biolactus; Bion Transit; Econormotil†; Gastrofloral†; Lactil; Perenteryl; ***China***: Bioflor (亿活); Ding Jun Sheng (定君生); Ju Ke (菊克); Lacteol Fort (乐托尔); Yan Hua (延华); ***Cz.***: Enterol; ***Denm.***: Paraghurt; Vivag; ***Fin.***: Lactophilus; Precosa; ***Fr.***: Bacilor; BioGaia; Bion Transit; Bioprotus; Gyno-Control; Gynophilus; Lacteol; Lactibiane Candisis; Lactibiane Protect; Lyobifidus; Normaflius; Orogyn; Ultra-Levure; ***Ger.***: Doderlein Med†; Gynophilus; Hylak N†; Hylak Plus†; InfectoDiarrstop LGG Mono; Lacteol; Lyseen; Paidoflor; Perenterol; Symbioflor 1; Vagiflor; ***Gr.***: Ultra-Levure; ***Hong Kong***: Bioflor; Lacteol; Reuteri; ***Hung.***: Enterol; Gynevac; Ovulobact; Symbioflor 1; ***India***: Babylac; Baclac; Base; Benspore; Bio 4; Cefocef-LB; Comensal; Darolac-IBS; Econorm; Flora-L; GNorm; GSLB; Lac-M; Lactiflora; Lactobacil; Lactogenes; Lactolus; Lactospore; Lactra; Lactrol; Lacven; LBDix; Lexicom; Medalac; Myconip; Sporlac; ***Indon.***: BioGaia; Geebio; Lacbon; Rillus; ***Ital.***: Bactocin; Bioflorin; Codex; Dicoflor; Bcocillin; Ecoflorina; Eptavis; Giflorex; Inulac; Lacteol; Lactonorm; Probinul; Provag†; Regolact Plus; Reuflor; Softigyn; VSL 3; ***Mex.***: Biolactos; Floratil; Lacteol Fort; Lactipan; Lactocil†; Lactovita†; Liolactil; Neoflor; Sinuberase†; ***Norw.***: Precosa; ***NZ***: Blis K12 Throat Guard; ***Philipp.***: Floratil; Infloran; Pro-bio; ***Pol.***: EcoVag; Enterol; Lactovaginal; Lakcid; ***Port.***: Antibiophilus; Lacteol; UL 250; ***Rus.***: Bificol (Бификол); Bifidumbacterin (Бифидумбактерин); Bifinorm (Бифинорм); Ecofemin (Экофемин); Enterol (Энтерол); Gastropharm (Гастрофарм); IRS 19 (ИРС 19); Lactobacterin (Лактобактерин); Probifor (Пробифор); ***S.Afr.***: Actiflora†; Inteflora; ***Singapore***: BioGaia; DiarrStope; Lacteol; Pro-BIS; Protexin; Reutefene†; ***Spain***: Casenfilus; Lacteol; Lactofilus; Ultra-Levura; ***Swed.***: Precosa; Probiomax; Vivag; ***Switz.***: Bioflorin; Bioflorina; Florosan†; Lacteol; Lactoferment; Perenterol; Symbioflor 1; Ultra-Levure†; ***Thai.***: Bioflor; ***Turk.***: Perocur; Reflor; ***UK***: Bio Acidophilus; Biodophilus; Gum PerioBalance; Infacol Probiotic; ***Ukr.***: BioGaia (БиоГая); Bioselac (Биоселак); Enterol (Энтерол); Gynolakt (Гинолакт); Hylak (Хилак); Linbi (Линби); Normagut (Нормагут); Preema (Према); SolcoTrichovac (Солкотриховаг)†; ***USA***: Acidophilus; Align Daily Probiotic Supplement; Bacid; BioGaia; Culturelle; Florastor; Gerber Soothe Colic Drops; Intestinex; Kala; Lactinex; Lacto-Key; MoreDophilus; Pro-Bionate; Superdophilus; ***Venez.***: Florcidin; Florestor; Lacteol; Lactobacilos; Liolactil; Proflor.

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

Promelase (pINN) ⊗

EC 3.4.21.63; Oryzin; Promelasa; Promélase; Promelasum; Seaprose S; Промеказа.

CAS — 9074-07-1.

Profile

Promelase is an alkaline protease derived from *Aspergillus melleus*. It has been taken orally in doses of 30 to 90 mg daily for its supposed benefit in oedema and inflammation associated with trauma, infection, and surgical procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Altan; Flaminase.

Pronase ⊗

Проназа.

Profile

Pronase is a mixture of proteinases obtained from *Streptomyces griseus*. It is used for inflammation associated with trauma, chronic sinusitis, and surgical procedures and as a mucolytic for tenacious sputum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Empynase.

Propolis

Bee Glue; Propóleo; Própolis; Прополис.

UNII — 6Y8XYV2NOF.

Profile

Propolis is a resinous substance collected by bees, mainly, at least in temperate climates, from poplar buds (see also p. 2594.2) and to a lesser extent from conifers. It is mixed with wax by bees and used in the construction and maintenance of their hives. Propolis is composed of resins, balsams, essential and aromatic oils, and pollen, although

the exact proportions of each varies from region to region, bee species, and local flora, therefore making standardisation of propolis for medicinal use difficult. Propolis has been reported to have anti-inflammatory and antimicrobial properties. It has been used as a nutritional supplement and in preparations for coughs, mouth disorders, and skin disorders. It has been used as an ointment for the relief of symptoms of herpes labialis. Propolis has also been used in cosmetics and varnishes.

Effects on the kidneys. Acute renal failure associated with 4 months of use of propolis in a homoeopathic product (exact form and dose not reported) developed in a 3-year-old boy with a history of gluten enteropathy.[1] Creatinine concentrations returned to normal after stopping propolis.

1. Health Canada. Propolis: suspected association with renal failure. *Can Adverse React News* 2009; 19(1): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n1-eng.pdf (accessed 05/02/09)

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including propolis, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Propoleos; Sweety; *Chile*: Propolkit; *Ger.*: Propolisept-Salbe†; *Hung.*: Propur; *Ital.*: Golapiol; Oral Spray†; Pro-Gola; Propociclina; Propolcream†; Propolgel; *Pol.*: Apizel; Propolan†; Propolisan; Propolisol; *Rus.*: Proposol (Пропосол); *Swed.*: Herstat†; *USA*: Probax.

Multi-ingredient Preparations. *Arg.*: Farinop; *Braz.*: Malvatricin Natural Organic†; *Chile*: Propolis C; Propolkit; Propolkit; Timuss-Kit (sin azucar); Timuss-Kit; *Fr.*: Alvityl Defenses; Duab; Olioseptil Gorge-Larynx; Olioseptil Gorge-Larynx; Propargile; *Hong Kong*: Vita Coldycin Echinacea Plus†; *Hung.*: Aranyer Elleni; *Indon.*: Imumax; Neoboost Kids; Opinacea; Opinacea; *Ital.*: Actires; Altuss; Apistress; Biogreen; Body Guard; Bron 6; Coryfin C senza Zucchero; Emoform Alifresh; Faringel; Fosfarsile Forte; Golapiol C; Immumil Plus†; Influpiol C; Influtux; Keratolip; Neo-Stomygen; Nepiros; Probigol; Promix 3; Propast; Valcap; Valda Propoli†; Valda Propoli; *Pol.*: Scaldex; *Rus.*: Proposol-N (Пропосол-Н); Prostopine (Простопин); *Singapore*: Arkopharma Propolis Spray; *Turk.*: Immuzinc; *UK*: Sinose; *Ukr.*: Apibact (Апибакт); Apiprost (Апипрост); Proalor (Проалор)†.

Homoeopathic Preparations. *Ger.*: Propolisept Urtinktur.

Proteases

Peptidasas; Peptidasen; Peptidases; Peptidazès; Peptidbindungshydrolasen; Proteaasit; Proteaser; Protéases; Proteasi; Proteázok; Proteazy; Proteázy; Proteinases.

Profile

Proteases are enzymes that hydrolyse proteins. They are found in all living organisms and are involved in a wide range of biological and physiological processes. Proteases are an important constituent of pancreatic enzymes (p. 2579.3) and preparations containing proteases have been used in gastrointestinal disorders. Proteases such as collagenase (p. 2484.1) have been used for wound debridement. Proteases have also been used for instrument disinfection and contact lens care. Some proteases have been promoted for pain and inflammation and for auto-immune disorders, but such uses are not established.

Reviews.

1. Craik CS, *et al.* Proteases as therapeutics. *Biochem J* 2011; 435: 1–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Flaviastase†; *USA*: PAN-2400†.

Multi-ingredient Preparations. *Arg.*: Dom-Polienzim; Polienzim; *Canad.*: Multi-Zyme†; Synergy Defense; *Cz.*: Iruxol Mono; *Fin.*: Iruxol Mono; *Fr.*: Aniosyme†; *Hong Kong*: Enzyplex; *Hung.*: Iruxol Mono†; *India*: Digestomen-P; Farizym; Leno-EZ; *Indon.*: Enzyplex; Excelase-E; Vitazym; Xepazym; *Irl.*: Iruxol Mono; *Malaysia*: Enzyplex†; Iruxol Mono; *S.Afr.*: Iruxol Mono; *Singapore*: Enzyplex; *Spain*: Iruxol Mono; *Thai.*: Enzyplex†; *USA*: Digex†; Enzyme; Ku-Zyme†; Kutrase†; Pangestyme†; *Venez.*: Festal Reformulado.

Prostaglandins

Простагландины.

Profile

The prostaglandins, along with thromboxanes and leukotrienes, are all derived from 20-carbon polyunsaturated fatty acids and are collectively termed *eicosanoids*. In man, the most common precursor is arachidonic acid (eicosatetraenoic acid; p. 2446.1) whereas eicosapentaenoic acid is a predominant precursor in fish and marine animals.

Arachidonic acid is released from cell-membrane phospholipids by the enzyme phospholipase A_2 and is then rapidly metabolised by several enzymes, the major ones being cyclo-oxygenase (prostaglandin synthetase) and lipoxygenase (see Figure 1, below). The prostaglandins, thromboxanes, and prostacyclin (sometimes collectively termed *prostanoids*) all contain ring structures and are products of arachidonic acid oxidation by cyclo-oxygenase, an enzyme with 2 isoforms (COX-1 or COX-2) widely distributed in cell membranes.

The leukotrienes are products of the lipoxygenase pathway; arachidonic acid is metabolised by lipoxygenases to hydroperoxyeicosatetraenoic acids, which are then further metabolised to leukotrienes.

The initial step in the cyclo-oxygenase pathway is the formation of cyclic endoperoxide prostaglandin G_2 (PGG_2), which is then reduced to the endoperoxide prostaglandin H_2 (PGH_2). Prostaglandin H_2 is then converted to the primary prostaglandins prostaglandin D_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$, to thromboxane A_2 (TXA_2) via the enzyme thromboxane synthetase, or to prostacyclin (PGI_2) via the enzyme prostacyclin synthetase. These products are further metabolised and rapidly inactivated in the body.

The secondary prostaglandins, prostaglandin A_2 (PGA_2), prostaglandin B_2 (PGB_2), and prostaglandin C_2 (PGC_2) are derived from prostaglandin E_2, but are formed during extraction and probably do not occur biologically.

The prostaglandins are all derivatives of the carbon skeleton 7-(2-octilcyclopentyl)heptanoic acid (also known as prostanoic acid). All natural prostaglandins have a double bond at position 1,2 and a hydroxyl group at position 3 of the octil side-chain. Depending on the substitutions on the cyclopentane ring, the main series of prostaglandins are distinguished by the letters A, B, C, D, E, and F; the members of each series are further subdivided by subscript numbers that indicate the degree of unsaturation in the side-chains—hence, those derived from eicosatrienoic acid (dihomo-γ-linolenic acid) have the subscript 1, those derived from arachidonic acid have the subscript 2, and those derived from eicosapentaenoic acid have the subscript 3. In man, only prostaglandins of the '2' series appear to be of physiological importance. Thromboxane A_2 has an oxane rather than a cyclopentane ring; it is chemically unstable and breaks down to thromboxane B_2. Prostacyclin has a double-ring structure and breaks down to 6-keto-prostaglandin $F_{1\alpha}$.

Endogenous prostaglandins are autacoids; they can be formed by virtually all tissues and cells in response to a variety of stimuli, have many **actions**, and are involved in the regulation of virtually all biological functions. Prostaglandins appear to act through various receptor-mediated mechanisms. Some of their effects are mediated within cells by activation or inhibition of adenylate cyclase and the regulation of cyclic adenosine monophosphate production. At one time prostaglandin E_1 and prostaglandin $F_{2\alpha}$ were thought to be of paramount importance, but with the discovery of thromboxane A_2, prostacyclin, and the leukotrienes it was realised that these primary prostaglandins belong to a large family of physiologically active eicosanoids. Thromboxane A_2 induces platelet aggregation and constricts arterial smooth muscle whereas prostacyclin causes vasodilatation and prevents platelet aggregation; the balance between these opposing actions has an important role in the regulation of intravascular platelet aggregation and thrombus formation. The leukotrienes are important mediators of inflammation.

The pharmacological properties of prostaglandins are wide-ranging and include contraction or relaxation of smooth muscle in the blood vessels, bronchi, uterus, and gastrointestinal tract; inhibition of gastric acid secretion; and effects on platelet aggregation, the endocrine system, and metabolic processes.

Individual prostaglandins vary greatly in their activities and potencies; their actions also depend on the animal species, on the tissues in which they are acting, and on the concentration present, and entirely opposite actions may be elicited with very small structural changes in the molecule.

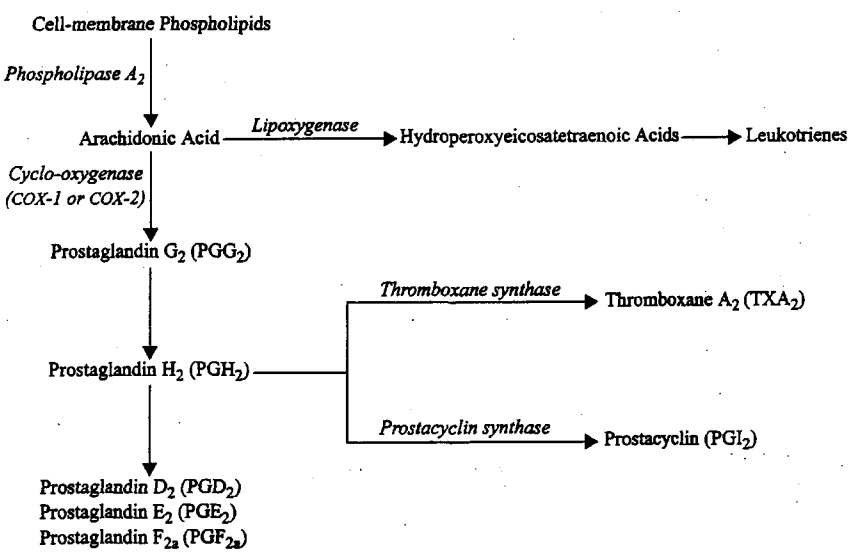
The diverse **clinical applications** of prostaglandins reflect their wide-ranging physiological and pharmacological properties. Synthetic analogues have been developed with the aim of obtaining compounds that are more stable, have a longer duration of action, and a more specific effect. Applications include:

- softening and dilating the cervix and for uterine stimulation, e.g. dinoprost (prostaglandin $F_{2\alpha}$) (p. 2133.3) and its analogue carboprost (p. 2133.1); dinoprostone (prostaglandin E_2) (p. 2134.1) and its analogue sulprostone (p. 2145.3); and gemeprost (p. 2137.2) and misoprostol (p. 2140.3), analogues of prostaglandin E_1
- vasodilators and inhibitors of platelet aggregation, e.g. alprostadil (prostaglandin E_1) (p. 2352.2) and its analogue limaprost (p. 1420.3); and epoprostenol (prostacyclin) (p. 1374.3) and its analogue iloprost (p. 1408.1)
- inhibition of gastric acid secretion and protection of the gastrointestinal mucosa, e.g. misoprostol (p. 2140.3)
- glaucoma treatment, e.g. bimatoprost (p. 2004.2), latanoprost (p. 2008.1), travoprost (p. 2012.1), and unoprostone (p. 2013.1)
- as luteolytics (causing regression of the corpus luteum in the ovary) in veterinary medicine, e.g. synthetic analogues of prostaglandin $F_{2\alpha}$.

References.

1. Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. *N Engl J Med* 1979; 300: 1142–7.
2. Higgs GA, Vane JR. Inhibition of cyclo-oxygenase and lipoxygenase. *Br Med Bull* 1983; 39: 265–70.
3. Halushka PV, *et al.* Thromboxane, prostaglandin and leukotriene receptors. *Annu Rev Pharmacol Toxicol* 1989; 29: 213–39.
4. Smith WL, *et al.* Prostaglandin and thromboxane biosynthesis. *Pharmacol Ther* 1991; 49: 153–79.
5. O'Neill C. The biochemistry of prostaglandins: a primer. *Aust N Z J Obstet Gynaecol* 1994; 34: 332–7.
6. Wu KK. Molecular regulation and augmentation of prostacyclin biosynthesis. *Agents Actions Suppl* 1995; 45: 11–17.

Figure 1. Prostaglandin biosynthesis.



Protoporphyrin IX Disodium

Protoporfirina IX disódica; Protoporphyrin Disodium.
Disodium 7,12-diethenyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoate.
$C_{34}H_{32}N_4Na_2O_4$=606.6.
CAS — 50865-01-5 (protoporphyrin IX disodium); 553-12-8 (protoporphyrin IX).
UNII — 54N4UY1C7C.

Profile

Protoporphyrin IX disodium has been given orally for the treatment of impaired hepatic function associated with gallstones and cholecystitis.

Psilocin

4-Hydroxy-*NN*-dimethyltryptamine; Psilocina; Psilocyn.
3-(2-Dimethylaminoethyl)indol-4-ol.
$C_{12}H_{16}N_2O$=204.3.
CAS — 520-53-6.
UNII — CMS88KUW0G.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of psilocin or mushrooms containing psilocin:

1UP's; Abhort; Aborts; Alice; Benzies; Blue Rimmers; Boom-Dads; Boomers; Caps; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; God's flesh; Goombas; Gus; Jesus; Lalkas; Liberty caps; Little smoke; Magic mushroom; Magic Mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushrooms; Musk; Pizza Toppings; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Toads; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Psilocybine *(BAN, rINN)*

CY-39; 4-Phosphoryloxy-*NN*-dimethyltryptamine; Psilocibina; Psilocybin; Psilocybinum; Psilosybiini; Псилоцибин.
3-(2-Dimethylaminoethyl)indol-4-yl dihydrogen phosphate.
$C_{12}H_{17}N_2O_4P$=284.3.
CAS — 520-52-5.
UNII — 2RV7212BP0.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of psilocybine or mushrooms containing psilocybine:

1 UP's; Alice; Benzies; Blue caps; Blue Rimmers; Boom-Dads; Boomers; Booms; Buttons; Caps; Champ; Crumb Tarts; Cubes; FireWorks; Fun Gus; Fun Guys; Fungus; Funguys; God's flesh; Goombas; Gus; Hombrecitos; Jesus; Lalkas; Las mujercitas; Little smoke; Magic mushroom; Magic mushrooms; Marios; Mexican mushroom; Mexican mushrooms; Mucks; Muggers; Mush; Mushies; Mushroom soup; Mushroom tea; Mushrooms; Musk; Philosopher's Stones; Pizza toppings; Rooms; Sacre mushroom; Sacred mushroom; Sacred mushrooms; Shroomies; Shrooms; Silly putty; Simple Simon; Smurfhats; Teonanactl; Toads; Truffles; Umbrellas; Yellow Bentines; Zoomers; Zoomies.

Profile

Psilocin and psilocybine are indole alkaloids obtained from the sacred Mexican mushroom (teonanácatl), *Psilocybe mexicana* (Agaricaceae).

In the UK, psilocybine is present in the indigenous mushroom *Psilocybe semilanceata* (magic mushroom; liberty cap). Psilocybine is also present in other species of mushrooms including *Stropharia cubensis* and *Conocybe* spp.

Psilocybine has hallucinogenic and sympathomimetic properties similar to those of lysergide (p. 2547.1). It is less potent than lysergide and its hallucinogenic effects last for up to 6 hours. There is evidence to suggest that psilocybine is converted to the active form psilocin in the body. It has no therapeutic use.

Pulegium Oil

Aceite esencial de menta poleo; Aceite esencial de poleo-menta; Pennyroyal Oil; Poleo, aceite esencial de; Масло Мяты Болотной.
UNII — AK8SU7Y3MV.

Uses and Administration

Pulegium oil is a volatile oil distilled from pennyroyal herb, *Mentha pulegium* (Labiatae), containing pulegone ($C_{10}H_{16}O$ = 152.2). It was formerly used as an emmenagogue. Pulegium is reported to have insect repellent activity.

Adverse Effects

Severe toxic effects have followed use of pulegium oil as an abortifacient with convulsions, hepatotoxicity, and death.

Severe hepatotoxicity accompanied by seizures occurred in 2 infants each of whom had received herbal teas containing pulegium oil.[1] In one of the infants multiple organ failure developed, and fulminant hepatic failure with hepatocellular necrosis and cerebral oedema proved fatal. A further 4 cases of toxicity associated with ingestion of pulegium oil have been reported;[2] three of the cases were adult patients who had ingested either herbal teas to induce menses (2 cases) or a herbal extract as an abortifacient (1 fatality), and the fourth was a 22-month old child who had ingested the oil.

1. Bakerink JA, *et al.* Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. *Pediatrics* 1996; 98: 944–7.
2. Anderson IB, *et al.* Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. *Ann Intern Med* 1996; 124: 726–34.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Pulmonary Surfactants

Tensioactivos pulmonares; Лёгочные Сурфактанты.

Description. Pulmonary surfactants are mixtures consisting mainly of phospholipids and surfactant proteins that are used to replace deficient endogenous lung surfactants. Several preparations have been studied including:

- natural human surfactant obtained from amniotic fluid or biosynthetic material
- natural animal-derived surfactants, which are bovine or porcine lung extracts that may be modified by the addition of synthetic surfactants, as in the case of beractant, or unmodified, as in the case of bovactant and calfactant
- synthetic or semisynthetic preparations, which may contain the phospholipid colfosceril palmitate, a major constituent of natural lung surfactants, in combination with other substances that aid spreading and absorption such as the synthetic peptide sinapultide.

Beractant *(BAN, USAN)*

A-60386X; Беractant.
CAS — 108778-82-1.
UNII — S866O45PKG.

Description. Beractant is a modified bovine lung extract containing mostly phospholipids, modified by the addition of colfosceril palmitate, palmitic acid, and tripalmitin.

The term Surfactant TA has been applied to a modified bovine lung surfactant.

Bovactant *(BAN)*

SF-R11; SF-RI1.
CAS — 151437-98-8.

Description. Bovactant is an extract of bovine lung containing about 92% of phospholipids, 3.2% of cholesterol, 0.6% of surfactant-associated hydrophobic proteins, and 0.4% of free fatty acid.

Calfactant *(BAN, USAN)*

CAS — 183325-78-2.
UNII — Q4K217VGA9.

Description. Calfactant is an unmodified calf lung extract that includes mostly phospholipids and hydrophobic surfactant-specific proteins (SP-B and SP-C).

Colfosceril Palmitate *(BAN, USAN, rINN)*

129Y83; Colfosceril, Palmitate de; Colfoscerili Palmitas; Colfoscerilo, palmitato de; Dipalmitoylphosphatidylcholine; DPPC; Palmitato de colfoscerilo; Колфосцерила Пальмитат.
1,2-Dipalmitoyl-*sn*-glycero(3)phosphocholine.
$C_{40}H_{80}NO_8P$=734.1.
CAS — 63-89-8.
ATC — R07AA01.
ATC Vet — QR07AA01.
UNII — 319X2NFWQA (L-Dipalmitoylphosphatidylcholine); 2W15RT5V7V (DL-Dipalmitoylphosphatidylcholine).

Description. Colfosceril palmitate is a phospholipid which forms an important constituent of natural and many synthetic pulmonary surfactant compounds.

Lucinactant *(USAN)*

API-02; ATI-02; KL$_4$-surfactant.
CAS — 825600-90-6.

Description. Lucinactant is a mixture of sinapultide, colfosceril palmitate, sodium palmitoyloleaylphosphatidyl glycerol, and palmitic acid.

Poractant Alfa *(BAN)*

Пораktant Альфа.
CAS — 129069-19-8.
UNII — KE3U2023NP.

Description. Poractant alfa is an extract of porcine lung containing not less than 90% of phospholipids, about 1% of hydrophobic proteins (SP-B and SP-C), and about 9% of other lipids.

Pumactant *(BAN)*

Artificial Lung Expanding Compound; Пумактант.
CAS — 258856-56-3.

Description. Pumactant is a mixture of colfosceril palmitate and phosphatidyl glycerol (2-oleoyl-1-palmitoyl-*sn*-glycero(3)phospho(1)-*sn*-glycerol) in the proportion 7:3.

Sinapultide *(USAN, rINN)*

ATI-01; KL-4 Peptide; Sinapultida; Sinapultidum; Синапультид.
CAS — 138531-07-4.
UNII — 040X3AX99T.

Description. Sinapultide is a synthetic peptide that mimics the actions of human surfactant protein B, an important constituent of natural pulmonary surfactant compounds.

Uses and Administration

Pulmonary surfactants are compounds with surface active properties similar to those natural substances in the lung that help to maintain the patency of the airways by reducing the surface tension of pulmonary fluids. Exogenous pulmonary surfactants are used in the treatment of neonatal respiratory distress syndrome (see p. 2600.1) in premature infants, and may also be given for prevention in infants considered to be at risk of developing the syndrome. Doses vary, but most pulmonary surfactants are given in recommended doses of 100 to 200 mg phospholipids per kg birth-weight; a suggested dose for colfosceril palmitate has been 67.5 mg/kg. For the treatment of overt neonatal respiratory distress syndrome, the initial dose is given as soon as possible after diagnosis, while for prevention it is given as soon as possible after birth. It is given as a suspension via an endotracheal tube to intubated neonates receiving mechanical ventilation. Manufacturers may recommend regimens with or without disconnection from the ventilator. Repeat doses may be given if necessary, although the number of doses and the dosage interval varies.

Pulmonary surfactants have also been tried in bronchopulmonary dysplasia in premature infants, meconium aspiration syndrome in newborn infants, and acute respiratory distress syndrome in adults.

Reviews.

1. Stevens TP, Sinkin RA. Surfactant replacement therapy. *Chest* 2007; 131: 1577–82.
2. Sweet DG, Halliday HL. The use of surfactants in 2009. *Arch Dis Child Educ Pract Ed* 2009; 94: 78–83.

Administration in children. Doses of pulmonary surfactants for the treatment of neonatal respiratory distress syndrome are given under Uses and Administration above.

Acute respiratory distress syndrome. Pulmonary surfactants have been investigated for acute respiratory distress syndrome (p. 1599.3). In adults, they have been given by intrabronchial instillation[1] or nebulisation[2-4] but results have been largely disappointing. Sequential bronchopulmonary segmental lavage with a synthetic surfactant has also been tried[5] and appeared to be well tolerated. Endotracheal poractant alfa moderately improved oxygenation in some children with severe acute respiratory distress syndrome secondary to pulmonary or systemic disease.[6] Pulmonary surfactants have also been used in two infants in the management of pneumonitis and acute respiratory distress syndrome after accidental hydrocarbon aspiration.[7,8]

1. Hasiam PL, *et al.* Surfactant replacement therapy in late-stage adult respiratory distress syndrome. *Lancet* 1994; 343: 1009–11.
2. do Campo JL, *et al.* Natural surfactant aerosolisation in adult respiratory distress syndrome. *Lancet* 1994; 344: 413–14.
3. Weg JG, *et al.* Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress syndrome. *JAMA* 1994; 272: 1433–8.
4. Anzueto A, *et al.* Aerosolized surfactant in adults with sepsis-induced respiratory distress syndrome. *N Engl J Med* 1996; 334: 1417–21.

5. Wiswell TE, *et al.* Bronchopulmonary segmental lavage with Surfaxin (KL4-Surfactant) for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **160**: 1188–95.
6. López-Herce J, *et al.* Surfactant treatment for acute respiratory distress syndrome. *Arch Dis Child* 1999; **80**: 248–52.
7. Horoz OO, *et al.* Surfactant therapy in acute respiratory distress syndrome due to hydrocarbon aspiration. *Singapore Med J* 2009; **50**: e130–2.
8. Mastropietro CW, Valentine K. Early administration of intratracheal surfactant (calfactant) after hydrocarbon aspiration. Abstract: *Pediatrics* 2011; **127**: 1170. Full version: http://pediatrics.aappublications.org/content/127/6/e1600.full.pdf (accessed 23/11/12)

Drowning. Reference to the use of colfosceril palmitate in the management of a 9-year-old rescued after near drowning.[1]

1. McBrien M, *et al.* Artificial surfactant in the treatment of near drowning. *Lancet* 1993; **342**: 1485–6.

Meconium aspiration syndrome. Meconium aspiration syndrome produces respiratory distress in infants born at term or later and is a consequence of airways obstruction, chemical pneumonitis, disturbances of pulmonary surfactant, and pulmonary hypertension. Bolus intratracheal doses of exogenous pulmonary surfactant may reduce the need for extracorporeal membrane oxygenation in infants with moderate to severe respiratory failure,[1] and promising results have been reported in studies involving bronchoalveolar lavage of the lungs with diluted surfactant.[2] However, there are few controlled studies of these treatments and further comparative investigations are needed.

1. El Shahed AI, *et al.* Surfactant for meconium aspiration syndrome in full term/near term infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 03/01/13).
2. Choi HJ, *et al.* Surfactant lavage therapy for meconium aspiration syndrome: a systematic review and meta-analysis. *Neonatology* 2012; **101**: 183–91.

Neonatal respiratory distress syndrome. Pulmonary surfactants improve the clinical outcome of premature infants with neonatal respiratory distress syndrome (p. 1608.3). A systematic review[1] of 9 randomised studies conducted in the 1990s concluded that intubation and prophylactic surfactant therapy in infants thought to be at risk of developing respiratory distress syndrome (RDS) has a greater effect on improvements in clinical outcome than intubation and surfactant given to infants with established RDS; prophylactic surfactant was shown to decrease the risk of pneumothorax, pulmonary interstitial emphysema, and mortality. Furthermore, multiple doses of surfactant for prophylaxis or treatment were shown to have greater benefits than a single dose in a systematic review[2] of 3 studies. Starting treatment when there were early signs of respiratory distress also reduced the risk of both short-term and longer-term lung injury.[3]

However, mechanical ventilation can contribute to lung injury in premature infants with RDS, and a systematic review[4] of 6 randomised studies concluded that giving early surfactant therapy with extubation to nasal continuous positive airway pressure (CPAP) was associated with less need for mechanical ventilation, a lower incidence of bronchopulmonary dysplasia, and fewer air leak syndromes compared with selectively giving surfactant later when RDS has worsened requiring mechanical ventilation. Later studies undertaken when maternal antenatal corticosteroid prophylaxis and CPAP had become routine found that early stabilisation on CPAP, with surfactant only given to infants needing intubation, was associated with a reduced risk of chronic lung disease or death when compared with prophylactic surfactant.[1] The administration of intratracheal surfactant through a temporary thin catheter to infants receiving CPAP has also been reported, and in a randomised study of 220 infants this method was associated with a reduced need for mechanical ventilation compared with CPAP alone.[5]

1. Rojas-Reyes MX, *et al.* Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2012 (accessed 09/01/13).
2. Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 09/01/13).
3. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 11. Chichester: John Wiley; 2012 (accessed 09/01/13).
4. Stevens TP, *et al.* Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/01/13).
5. Göpel W, *et al.* German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011; **378**: 1627–34.

Adverse Effects and Precautions

Surfactant therapy may be associated with an increased risk of pulmonary haemorrhage, especially in more premature infants. Therapy should only be given where there are adequate facilities for ventilation and monitoring. Rapid chest expansion and improvement of oxygenation may follow successful treatment, and peak ventilatory pressure and inspired oxygen concentration may need to be reduced promptly to avoid the risk of pneumothorax and hyperoxaemia. A transient decrease in brain electrical activity has been reported in neonates given surfactant but its significance is unknown. Transient bradycardia and oxygen desaturation have also been reported. Giving surfactant has occasionally been associated with obstruction of the endotracheal tube by mucus.

While surfactant therapy is clearly associated with an increased risk of pulmonary haemorrhage,[1-4] meta-analysis suggests that the risk is small compared with the benefits.[1] However, neonates who do develop moderate or severe pulmonary haemorrhage after surfactant therapy are at increased risk of death or short-term morbidity.[5] Haemodynamic changes associated with surfactant therapy or consequent pulmonary haemorrhage may also predispose premature infants to intracranial (periventricular) haemorrhage.[5,6] Early preventive use of surfactant in very low birth-weight infants may be associated with a poorer neurodevelopmental outcome,[7] although a long-term follow-up study[8] of premature infants born in the surfactant era concluded that these children had similar neurodevelopmental outcomes to such children born before the introduction of surfactant therapy. Decreased brain electrical activity has been reported after surfactant treatment.[9]

The rate of instillation of surfactant may be significant: one study,[10] in which the apparatus was adapted so that mechanical ventilation could continue while giving surfactant, found that rapid instillation over a 5-minute period provoked a transient increase in cerebral blood flow velocity associated with an increase in carbon dioxide tension, compared with slow instillation over 15 minutes. Although the authors acknowledged that such changes were likely to be related to several factors, particularly the type of surfactant, they recommended that, until further data were available, instillation should take place slowly, over at least 15 to 20 minutes.

1. Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a meta-analysis. *J Pediatr* 1993; **123**: 603–10.
2. Majeed-Saidan MA, *et al.* Pulmonary haemorrhage in low-birthweight babies. *Lancet* 1993; **341**: 120.
3. Rogers D. Pulmonary haemorrhage, surfactant, and low-birthweight babies. *Lancet* 1993; **341**: 698.
4. Pappin A, *et al.* Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. *J Pediatr* 1994; **124**: 621–6.
5. Pandit PB, *et al.* Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F40–F44.
6. Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: review of the literature and results of new analyses. *Pediatrics* 1993; **92**: 775–86.
7. Vaucher YE, *et al.* Outcome at twelve months of adjusted age in very low birthweight infants with lung immaturity: a randomized placebo-controlled trial of human surfactant. *J Pediatr* 1993; **122**: 126–32.
8. D'Angio CT, *et al.* Longitudinal, 15-year follow-up of children born at less than 29 weeks' gestation after introduction of surfactant therapy into a region: neurologic, cognitive, and educational outcomes. *Pediatrics* 2002; **110**: 1094–1102.
9. Hellström-Westas L, *et al.* Cerebroelectrical depression following surfactant treatment in preterm neonates. *Pediatrics* 1992; **89**: 643–7.
10. Saliba E, *et al.* Instillation rate effects of Exosurf on cerebral and cardiovascular haemodynamics in preterm neonates. *Arch Dis Child* 1994; **71**: F174–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Baby Fact B; Surfactante B; Survanta; *Austral.*: Curosurf; Exosurf†; Survanta†; *Austria*: Curosurf; *Belg.*: Curosurf; Survanta; *Braz.*: Alveofact; Curosurf; Survanta; *Canad.*: BLES; Survanta; *Chile*: Surfacur; Survanta; *China*: Curosurf (固尔苏); Ke Li Su (珂立苏); *Cz.*: Curosurf; Survanta†; *Denm.*: Curosurf; *Fin.*: Curosurf; *Fr.*: Curosurf; Survanta†; *Ger.*: Alveofact; Curosurf; Survanta†; *Gr.*: Alvofact; Curosurf; Exosurf; Survanta; *Hong Kong*: Survanta; *Hung.*: Curosurf; Survanta; *Indon.*: Survanta; *Irl.*: Curosurf; *Israel*: Curosurf; Infasurf; *Ital.*: Curosurf; *Jpn*: Surfacten; *Malaysia*: Curosurf; Survanta; *Mex.*: Exosurf†; Survanta; *Neth.*: Curosurf; Survanta; *Norw.*: Curosurf; *NZ*: Curosurf; Survanta; *Philipp.*: Newfactan; Survanta; *Pol.*: Alveofact†; Curosurf; Survanta; *Port.*: Curosurf; Survanta; *Rus.*: Alveofact (Альвеофакт); Curosurf (Куросурф); Surfactant-BL (Сурфактант-БЛ); *S.Afr.*: Curosurf†; Survanta†; *Singapore*: Survanta; *Spain*: Curosurf; Survanta; *Swed.*: Curosurf; *Switz.*: Curosurf; Survanta; *Thai.*: Curosurf; Survanta; *Turk.*: Alveofact; Curosurf; Survanta; *UK*: Curosurf; Survanta; *Ukr.*: Curosurf (Курсурф); Infasurf (Инфасурф); Suzacrin (Сузакрин); *USA*: Curosurf; Infasurf; Surfaxin; Survanta; *Venez.*: Survanta.

Pulsatilla

Anémona; Anémone pulsatille; Meadow Anemone; Pasque Flower; Пульсатилла.

CAS — 62887-80-3.

ATC Herb — HN05CM5023 (Pulsatilla vulgaris: herb); *HG01AW5001* (Pulsatilla vulgaris: herb); *HD08AW5003* (Pulsatilla vulgaris: herb); *HN05CM5022* (Pulsatilla pratensis: herb); *HA03WX5006* (Pulsatilla vulgaris: herb).

UNII — I76KB35JEV (Pulsatilla vulgaris).

Profile

Pulsatilla is the whole flowering plant of *Pulsatilla vulgaris* (*Anemone pulsatilla*) or *Pulsatilla pratensis* (Ranunculaceae). It has been used in herbal preparations for the treatment of conditions including nervous disorders, circulatory disorders, and gynaecological disorders and benign prostatic hyperplasia.

Homoeopathy

Pulsatilla has been used in homoeopathic medicines under the following names: Pulsatilla pratensis; Pulsatilla vulgaris; Pulsatilla nigricans; Puls.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Calmo†; Femi-Nan; *Austria*: Hustensaft Weleda; *Cz.*: Cicaderma; *Fr.*: Hepatoum; Histo-Fluine P; *Ger.*: Eviprostat N; Weleda Hustenelixier; *Indon.*: Eviprostat; *Jpn*: Eviprostat; *Port.*: Cicaderma; Stodal; *S.Afr.*: Cough Elixir†; *Singapore*: Eviprostat; *Switz.*: Elixir contre la toux†; *UK*: Anased; Menopause Relief; Period Pain Relief; Prementaid.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Childrens Cold and Flu Relief; Childrens Runny Nose Relief; Childrens Sleep; Earache Relief†; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Joint & Muscle Oral Spray†; Pain & Fever Relief; Respatona Chesty Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; Snore Eze; *Austria*: Apozema Allium Cepa compositum; Cepa Med Complex; Delufen; Echinacea-Cosmoplex; Euphorbium Compositum; Gastricumeel; Globuli gegen Schlafstorungen; Lakrima; Otodolor; Pascofemin; Pulsatilla Med Complex; Rhododendroneel; Schnarchex; Vensa; *Canad.*: Acne; Bioactiv E†; Calms Forte 4 Kids; Calnor†; Cat Complex†; Cicaderma†; Comp-Drops 9†; Coryzalia; Cough & Cold; Cruroheel S†; Detox L37; Earache; Echinacea Compositum; Euphorbium Compositum; Euphorbium Compositum; Homeo-Form G†; Homeo-Form R†; Homeodel 21†; Hylands Formula MC; Hylands Formula S; Hylands Menstrual Cramps†; Hylands Sinus†; Indigestion†; Infilex†; Kids Allergies; Men Complex†; Rhinar†; Roxalia; Sinus; Stodal; Travel Sickness; Viburcol; *Chile*: Arnica Hamamelis Compuesta; Bioactiv A; Bioactiv E; Calcarea fluor Compuesta; Ikoplex No 18; *Cz.*: Coryzalia; Euphorbium Compositum; Homeogene 9; Hormeel S; Stodal; Viburcol; Ypsiloheel; *Fr.*: Abbe Chaupitre no 20†; Abbe Chaupitre no 30†; Abbe Chaupitre no 35†; Abbe Chaupitre no 64†; Abbe Chaupitre no 7; Abbe Chaupitre no 82†; Agnus Castus Complexe No 2†; Angipax; Arthro-Drainol; Berberis Complexe No 83; Cistus Canadensis Complexe No 86†; Cocculus Complexe No 73; Coryzalia; Drosera Complexe No 64; Formica Rufa Compose; Hamamelis Compose; Homeodose 20†; Homeogene 41†; Homeogene 9; Iodum Complexe No 118; Ipeca Compose; Millefolium Complexe No 7†; Myosotis Complexe No 63†; Nux Vomica Complexe No 49; Phytogargarisme†; Pulmo-Drainol†; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Sabal Serrulata Compose; Scrofularia Compose; Spirodrine; Staphysagria Complexe No 92†; Stodal; Stodal; Thuya Complexe No 37; Uva Ursi Complexe No 9; Vascodran; Veino-Drainol†; *Ger.*: Agnus castus comp†; Agnus femin; Aletris N Oligoplex; Aletris Oligoplex†; Antimas†; Cephaloplant†; Entzundungstropfen; Enuroplant N; Euphorbium comp SN; Femi-cyl L Ho-Len-Complex; Feminon N; Gastro-Plantin N†; Hewelymphon N†; Infifer N; Mucosa compositum; Neuroselect; Otimed; Pascofemin spasmo; Pascofemin; Prostata-Gastreu N R25; Pulsatirell; Rheuma-Hevert†; Schleimhaut-Komplex L Ho-Fu-Complex; Schwoneural N; Schworosin; Urotruw N; Varicylum N; Venen-Komplex Ho-Fu-Complex; Venoselect N; Viburcol N; Ypsiloheel N; *Hung.*: Coryzalia; Homeogene 9; Hormeel S; Stodal; Toxex; Viburcol; *Neth.*: Akutur spag; Coryzalia; Echinacea comp; Euphorbium comp; Gastricumeel; Gynaelite; Homeocare Cyclo; Homeocare neusspray; Homeogene 9†; Hormeel H; Kind 0-3 Chamodent; Kind 0-6 Rinikind; Kruidvat Homeopathie Neusspray†; Mucosa comp H; Nervofleur; Nisyspray; Oteel H; Pulsatilla comp; Sinufleur; Stodal; Toxex; Viburcol H; *Port.*: Coryzalia; Homeogene 9; *Rus.*: Aphlubin-Naze (Афлубин-Назе); Cicaderma (Цикалерма); Coryzalia (Коризалия); Delufen (Делуфен); Dysmenorm (Дисменорм); Hormeel SN (Гормель СН); Ruta-Plus (Рута-Плюс); Stodal (Стодаль); Vensa (Венза); *S.Afr.*: Euphorbium Compositum S†; Viburcol; *Switz.*: Coryzalia; Gastricumeel; Homeogene 9; Menstruasan; Multiplex 1; Nelsons Sinusit†; Regenaplex Nr 86a; Regenaplex Nr. 31a; Regenaplex Nr. 31c; Regenaplex Nr. 49a; Regenaplex Nr. 71b; Stodal; Viburcol N; *UK*: Cough Elixir; *Ukr.*: Coryzalia (Коризалия); Delufen (Делуфен); Dentokind (Дентокинд); Dysmenorm (Дисменорм.); Incena (Инцена); Stodal (Стодаль); *USA*: Yeast-Gard†.

Punarnava

Punarnaba; Пунарнава.

Profile

Punarnava is the fresh or dried plant *Boerhaavia diffusa* (*B. repens*) (Nyctaginaceae), containing an alkaloid, punarnavine. It has been used as a diuretic and for liver disorders, usually in the form of a liquid extract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Gecitral.

Multi-ingredient Preparations. *Hung.*: Herbadict; *India*: Abana; Agloliv; Arjin; Arjunin; Arthopack; Bonnisan; Calcury; Cystone; Cytozen; Diabecon; Distone; Distone; Evecare; Evecare; Flush; Flush; Geriforte; Gynoset; Hepaliv; Hipato-P; Imunocin; Li-Verve; Livasa; Livomyn; Livomyn; Livto; Liyurto; Lukol; Megacure-DS; Megacure-DS; Megacure-DS; Neeti; New-Livfit; Nobese; Obenyl; *Malaysia*: Bonnisan; *Rus.*: Bonjigar (Бонджигар); Dipana (Дипана); *Ukr.*: Bonjigar (Бонджигар); Eve Care (Ив Кер)†; Imunin (Имунин)†.

Homoeopathic Preparations. *Fr.*: Poconeol no 23†.

Pyricarbate *(rINN)*

Piricarbato; Pyricarbatum; Pyridinolcarbamate; Пирикарбат.
2,6-Pyridinediyldimethylene bis(methylcarbamate).
$C_{11}H_{15}N_3O_4$=253.3
CAS — 1882-26-4.
UNII — 81R511UV73.

Profile

Pyricarbate has been given orally in the treatment of atherosclerosis and other vascular disorders, hyperlipidaemias, and thromboembolic disorders. Adverse effects have included gastrointestinal disturbances and liver damage.

Pyrogen

Pyrogenium.

Profile

Pyrogen is produced from a mixture of lean beef and water left to stand for several weeks.

Homoeopathy

Pyrogen has been used in homoeopathic medicines under the following names: Pyrogenium; Pyrexin; Sepsin; Putrescinum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Echinacea-Cosmoplex; *Canad.*: Kids' Earache; *Cz.*: Galium; *Ger.*: metabiarex; Pyrogenium.

Quassia

Bitter Wood; Casia de Surinam; Cuasia; Cuasia surinamense; Leño amargo; Leño de Cuasia; Palo amargo; Palo de Cuasia; Quassia amara; Quassia Wood; Quassiae Lignum; Quassiaholz; Quina de Cayena; Квассия.
CAS — 76-78-8 (quassin); 76-77-7 (neoquassin).
ATC — P03AX04.
ATC Vet — QP53AX03.
ATC Herb — HP03AX5003 (Quassia amara: *wood*); *HP03BX5005* (Quassia amara: *wood*); *HP02WA5003* (Picrasma excelsa: *wood*); *HP02WA5004* (Quassia amara: *wood*); *HP03BX5004* (Picrasma excelsa: *wood*); *HA09WA5020* (Picrasma excelsa: *wood*); *HA09WA5021* (Quassia amara: *wood*); *HP03AX5002* (Picrasma excelsa: *wood*).
UNII — 02G7GY29MO (Quassia amara); *S5249Q85HW* (Quassia amara *wood*).

Profile

Quassia is the dried stem wood of Jamaica quassia, *Picrasma excelsa* (*Aeschrion excelsa*; *Picraena excelsa*) (Simaroubaceae), or of Surinam quassia, *Quassia amara* (Simaroubaceae). It has been used as a bitter. It was formerly given as an enema for the expulsion of threadworms and was applied for pediculosis. It may also be used as a flavour in food, drinks, and confectionery. Extracts of quassia or preparations containing its triterpenoid bitter principle quassin are used to denature alcohol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cuassicum Prevent; Life + Quality; Picutex.

Multi-ingredient Preparations. *Arg.*: Aulo Repelente De Piojos; Cuassicum; Puera Bicho†; Rep Locion Repelente; Uze Active; *Braz.*: Camomila; *Canad.*: Para-Gard; Para-Gone; *Fr.*: Quintonine†; Skin Nail; Spevin†; *Ital.*: Dekar 2†; *S.Afr.*: Essens Amara of Groen Amara; Versterkdruppels; *Switz.*: Stomacine; *UK*: Sanderson's Throat Specific.

Homoeopathic Preparations. *Fr.*: Gentiana Complexe No 33†; *Ger.*: Bomagall; Choanol N; Cholo 2-injektopas; Hepa-Loges N; Hepar-Hevert N; Leber Albin; Pankreaticum; Pankreaticum; Spasmo-Bomaleb†; *Switz.*: metaheptachol.

Quebracho

Quebracho Blanco; White Quebracho; Квебрахо Белое.
ATC Herb — HR03WA5001 (Aspidosperma quebracho-blanco: *bark*); *HN02BW5001* (Aspidosperma quebracho-blanco: *bark*); *HA09WA5003* (Aspidosperma quebracho-blanco: *bark*).
UNII — 5281340190.

NOTE. Do not confuse with trees belonging to the genus *Schinopsis* that may also be referred to as quebracho.

Profile

The bark of white quebracho, *Aspidosperma quebracho-blanco* (Apocynaceae) is used in herbal medicine for the treatment of respiratory disorders. It has also been used to reduce fever, as an antihypertensive, and as a flavouring agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Afrodor†; *Hung.*: Bronchicum; Bronchicum; *Pol.*: Bronchicum Eliksir†; *Rus.*: Afrodor (Афродор)†; Bronchicum (Бронхикум)†.

Homoeopathic Preparations. *Austria*: Tartephedreel; *Chile*: Similibus; *Switz.*: Regenaplex Nr. 24c.

Quinagolide Hydrochloride *(BANM, rINNM)*

CV-205-502 (quinagolide); Hidrocloruro de quinagolida; Quinagolida, hidrocloruro de; Quinagolide, Chlorhydrate de; Quinagolidi Hydrochloridum; SDZ-CV-205-502 (quinagolide); Хинаголида Гидрохлорид.
(±)-*N,N*-Diethyl-*N'*-[(3*R**,4a*R**,10a*S**)-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[*g*]quinolin-3-yl]sulfamide hydrochloride.
$C_{20}H_{33}N_3O_3S,HCl$=432.0
CAS — 87056-78-8 (quinagolide); 94424-50-7 (quinagolide hydrochloride).
ATC — G02CB04.
ATC Vet — QG02CB04.
UNII — 33474X943Y.

Uses and Administration

Quinagolide is a non-ergot dopamine D_2-agonist that has actions and uses similar to those of bromocriptine (p. 895.3). It is used in the treatment of disorders associated with hyperprolactinaemia (p. 2252.2).

Quinagolide is given as the hydrochloride, but doses are described in terms of the base; 27.3 micrograms of quinagolide hydrochloride is equivalent to about 25 micrograms of quinagolide. The initial dose, given orally once daily with food at bedtime, is 25 micrograms daily for 3 days. Doses are increased thereafter at 3-day intervals in steps of 25 micrograms until the optimal response is achieved, which is usually within the range of 75 to 150 micrograms daily. If doses greater than 300 micrograms daily are required, the daily dosage may be increased in steps of 75 to 150 micrograms at intervals of not less than 4 weeks.

Hyperprolactinaemia and prolactinomas. References.

1. Rohmet V, *et al.* Efficacy of quinagolide in resistance to dopamine agonists: results of a multicenter study. *Ann Endocrinol (Paris)* 2000; 61: 411–17.
2. Schultz PN, *et al.* Quinagolide in the management of prolactinoma. *Pituitary* 2000; 3: 239–49.
3. Barlier A, Jaquet P. Quinagolide—a valuable treatment option for hyperprolactinaemia. *Eur J Endocrinol* 2006; 154: 187–95.

Lactation inhibition. The routine use of dopamine agonists such as quinagolide is not recommended for the suppression of physiological lactation (see p. 2130.1).

Adverse Effects and Precautions

As for Bromocriptine, p. 896.3, although it is not an ergot derivative and does not seem to be associated with fibrotic reactions or vasoconstriction. Licensed product information contra-indicates the use of quinagolide in patients with hepatic or renal impairment; however, this is based on a lack of data in such patients.

Effects on mental function. For reports of daytime somnolence occurring in patients receiving dopamine agonists including quinagolide, see Effects on Mental Function, under Adverse Effects of Levodopa, p. 905.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinagolide 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 06/10/11)

Interactions

As for Bromocriptine, p. 899.1.

Pharmacokinetics

Quinagolide is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism to the *N*-desethyl analogue which is biologically active and the *N*, *N*-didesethyl analogue. Roughly equal amounts of a dose appear in the urine and the faeces; it is excreted in the urine as sulfate or glucuronide conjugates of quinagolide and its metabolites and in the faeces as the unconjugated forms. Protein binding has been reported to be about 90%. The elimination half-life of quinagolide at steady state is about 17 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Norprolac; *Austria*: Norprolac; *Belg.*: Norprolac; *Canad.*: Norprolac; *Cz.*: Norprolac; *Denm.*: Norprolac; *Fin.*: Norprolac; *Fr.*: Norprolac; *Ger.*: Norprolac; *Gr.*: Norprolac; *Hong Kong*: Norprolac; *Hung.*: Norprolac; *Israel*: Norprolac; *Mex.*: Norprolac; *Neth.*: Norprolac; *Norw.*: Norprolac; *NZ*: Norprolac; *Pol.*: Norprolac; *Port.*: Norprolac; *Rus.*: Norprolac (Норпролак); *S.Afr.*: Norprolac; *Singapore*: Norprolac; *Spain*: Norprolac; *Swed.*: Norprolac; *Switz.*: Norprolac; *Turk.*: Norprolac; *UK*: Norprolac; *Ukr.*: Norprolac (Норпролак).

Quinine and Urea Hydrochloride

Carbamidated Quinine Dihydrochloride; Chininum Dihydrochloricum Carbamidatum; Quinina y urea, hidrocloruro de; Urea-Quinine.
$C_{20}H_{24}N_2O_2,CH_4N_2O,2HCl,5H_2O$=547.5
CAS — 549-52-0 (anhydrous quinine and urea hydrochloride).

Profile

Quinine and urea hydrochloride has been used for the treatment of haemorrhoidal bleeding and anal fissure. It was formerly used as a local anaesthetic and for the therapeutic actions of quinine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Kinurea H.

Quinine Arsenite

Tris[(8α)-6'-methoxycinchonan-9(*R*)-ol] arsenite.
$(C_{20}H_{24}N_2O_2)_3AsH_3O_3$=1099.2
CAS — 94138-87-1.
UNII — 42QO5PONLM.

Profile

Quinine arsenite is a trivalent arsenic compound (see Arsenic Trioxide, p. 2448.1) and may also show toxicity related to its quinine component (p. 665.1).

Homoeopathy

Quinine arsenite has been used in homoeopathic medicines under the following names: Arsénite de quinine; Chininum arsenicosum.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Cefasinu; Dolo-Injektopas; Lycoaktin; Schworocor A; *Switz.*: Sinfrontal.

Quinine Ascorbate *(USAN)*

Quinina, ascorbato de; Quinine Biascorbate; Аскорбиново-кислый Хинин.
$C_{20}H_{24}N_2O_2,2C_6H_8O_6$=676.7
CAS — 146-40-7.
UNII — KAU4V10S2I.

Profile

Quinine ascorbate is a compound (2 : 1) of ascorbic acid with quinine. It has been used as an ingredient of preparations promoted as smoking deterrents.

Ramatroban *(BAN, rINN)*

BAY-U-3405; EN-137774; Ramatrobán; Ramatrobanum; Раматробан.
(*R*)-3-[3-(4-Fluorophenylsulphonylamino)-1,2,3,4-tetrahydrocarbazol-9-yl]propionic acid.
$C_{21}H_{21}FN_2O_4S$=416.5
CAS — 116649-85-5.
UNII — P1ALI72U6C.

Profile

Ramatroban is a thromboxane A_2 inhibitor that has been used for the treatment of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Baynas.

Ranibizumab *(BAN, USAN, rINN)*

Ranibizumabum; Ранибизумаб.
Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFAB V2 γ1-chain), disulfide with human-mouse monoclonal rhuFAB V2 κ-chain.
CAS — 347396-82-1.
ATC — S01LA04.
ATC Vet — QS01LA04.
UNII — ZL1R02VT79.

Uses and Administration

Ranibizumab is a recombinant humanised monoclonal antibody fragment related to bevacizumab (p. 747.1). It binds to vascular endothelial growth factor A (VEGF-A), which prevents VEGF-A binding to the receptors VEGFR-1 and VEGFR-2, thereby reducing endothelial cell proliferation, new blood vessel formation (neovascularisation) and vascular leakage. Ranibizumab is used in the treatment of (wet) age-related macular degeneration (AMD) (below), diabetic macular oedema and macular oedema secondary to retinal vein occlusion (see Macular Oedema, below), and pathologic myopia (below)

In AMD and macular oedema secondary to retinal vein occlusion, ranibizumab is given by intravitreal injection into the affected eye in a dose of 500 micrograms once a month. For diabetic macular oedema, UK licensed product information recommends a monthly intravitreal dose of 500 micrograms, but US product information suggests 300 micrograms once a month, stating that the higher dose provides no additional benefit.

For all indications, US product information recommends ongoing monthly treatment. However, for patients with AMD, ranibizumab therapy may be reduced to 1 injection every 3 months after the first 4 injections if monthly treatment is not feasible, although this is not as effective. In contrast, UK product information recommends that treatment should continue only until visual acuity is stable for 3 consecutive monthly assessments. However, treatment should not continue if there has been no improvement of visual acuity over the course of the first 3 injections in patients with macular oedema. After stabilisation, monitoring should continue monthly until loss of visual acuity due to AMD or macular oedema recurs. Monthly ranibizumab treatment should then be restarted and continued until visual acuity is again stable for 3 consecutive monthly assessments. UK information also recommends that the interval between injections should be at least 1 month.

When given with laser photocoagulation for diabetic macular oedema or macular oedema secondary to branch retinal vein occlusion, ranibizumab should be given at least 30 minutes after the photocoagulation.

In pathologic myopia a single intravitreal injection of ranibizumab 500 micrograms is given into the affected eye. If subsequent monitoring shows disease activity, further injections can be given at intervals of no less than one month. Many patients will need only one or two injections in the first year, but some will need more frequent treatment and therefore monitoring should be monthly for the first 2 months and at least every 3 months thereafter during the first year.

Antimicrobial eye drops should be used for 3 days before and 3 days after each injection of ranibizumab.

Age-related macular degeneration. Ranibizumab is given by intravitreal injection in the treatment of (wet) age-related macular degeneration (AMD) (p. 880.2). Vision loss was prevented and mean visual acuity improved in patients given ranibizumab monthly for 2 years compared with patients receiving sham injections.[1] Ranibizumab was also shown to be superior to verteporfin photodynamic therapy after 1 year[2] and 2 years of therapy.[3,4] Open-label extensions of these studies showed that ranibizumab was well tolerated over at least 4 years of treatment.[5] The use of both ranibizumab and photodynamic therapy over 2 years has been reported to be more effective than photodynamic therapy alone.[6,7]

Monthly injection during maintenance therapy has produced the best results for visual acuity in clinical studies. Regular monitoring with flexible but less frequent dosing may be used when a monthly regimen is not possible, but is likely to be less effective.[8]

For results of a comparative study of the use of ranibizumab and bevacizumab in this disease, see Age-related Macular Degeneration, under Bevacizumab, p. 747.2.

1. Rosenfeld PJ, *et al.* for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1419–31.
2. Brown DM, *et al.* for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1432–44.
3. Brown DM, *et al.* ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009; 116: 57–65.
4. Bressler NM, *et al.* for the ANCHOR Research Group. Improved vision-related function after ranibizumab vs photodynamic therapy: a randomized clinical trial. *Arch Ophthalmol* 2009; 127: 13–21.
5. Singer MA, *et al.* HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2012; 119: 1175–83.
6. Heier JS, *et al.* FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. *Arch Ophthalmol* 2006; 124: 1532–42. Correction. *ibid.* 2007; 125: 138.
7. Antoszyk AN, *et al.* FOCUS Study Group. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am J Ophthalmol* 2008; 145: 862–74.
8. Mitchell P, *et al.* Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *Br J Ophthalmol* 2010; 94: 2–13.

Myopia. Intravitreal injection of ranibizumab has been reported to improve visual acuity in patients with choroidal neovascularisation secondary to pathologic myopia followed up for one[1,2] to 3 years;[3,4] retreatment was performed if monitoring showed persistent or new disease activity.

1. Vadalà M, *et al.* Is ranibizumab effective in stopping the loss of vision for choroidal neovascularisation in pathologic myopia? A long-term follow-up study. *Br J Ophthalmol* 2011; 95: 657–61.
2. Lorenzo D, *et al.* Intravitreal ranibizumab for choroidal neovascularization secondary to pathological myopia: 12-month follow-up. *Ophthalmologica* 2011; 226: 103–9.
3. Franqueira N, *et al.* Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab. *Ophthalmologica* 2012; 227: 39–44.
4. Hefner L, *et al.* Three years follow-up results of ranibizumab treatment for choroidal neovascularization secondary to pathologic myopia. *Klin Monbl Augenheilkd* 2013; 230: 401–4.

Macular oedema. Intravitreal ranibizumab may be used in the treatment of diabetic macular oedema (see Diabetic Eye Disease, p. 464.2). It can improve visual acuity and reduce macular oedema, and retinopathy is less likely to worsen and more likely to improve. The need for laser procedures may also be reduced.[1,2] Monthly doses of 300 and 500 micrograms have produced similar results, but these studies comparing ranibizumab treatment with sham injections for 2 years were not designed to compare the two doses.[1] Ranibizumab appeared to be more effective than laser photocoagulation, but the combination may be no better than ranibizumab alone; follow-up studies are ongoing.[2]

Improved visual acuity and reduced macular oedema were also found in studies of intravitreal ranibizumab given for 6 months to treat macular oedema caused by branch or central retinal vein occlusion.[3-5] Ranibizumab also accelerated the clearance of retinal haemorrhage. However, recurrent or persistent disease was common during subsequent observation, necessitating repeat treatment as required to maintain benefit.[3,4,6]

1. Nguyen QD, *et al.* RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; 119: 789–801.
2. Frampton JE. Ranibizumab: in diabetic macular oedema. *Drugs* 2012; 72: 509–23.
3. Brown DM, *et al.* Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology* 2011; 118: 1594–1602.
4. Campochiaro PA, *et al.* Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology* 2011; 118: 2041–9.
5. Garnock-Jones KP. Ranibizumab: in macular oedema following retinal vein occlusion. *Drugs* 2011; 71: 455–63.
6. Heier JS, *et al.* Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology* 2012; 119: 802–9.

Adverse Effects and Precautions

Ranibizumab is contra-indicated in patients with active or suspected ocular or periocular infections, or active severe intra-ocular inflammation.

Adverse effects relating to the injection procedure include intra-ocular inflammation, endophthalmitis, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Raised intra-ocular pressure has been reported within 60 minutes of injection and patients should be monitored and managed appropriately. Patients should also be monitored for signs of infections for a week after the procedure. Common but less serious ocular adverse effects include red eye, conjunctival or retinal haemorrhage, dry eye, blepharitis, eye pruritus, eye pain, vitreous floaters, eye irritation, increased lachrymation, and the sensation of a foreign body in the eye. Temporary visual disturbances have also been reported and patients should be advised not to drive or operate machinery until these have subsided.

Non-ocular adverse effects that have been reported include headache, nausea, arthralgia, nasopharyngitis, cough, bronchitis, and anaemia. Arterial thromboembolic events are a theoretical possibility following intravitreal use of vascular endothelial growth factor inhibitors. Ranibizumab should not be given concurrently with other inhibitors of vascular endothelial growth factor A (VEGF-A).

References.

1. Schmucker C, *et al.* Intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a safety review. *Br J Ophthalmol* 2011; 95: 308–17.

Effects on the cardiovascular system. Arterial thromboembolic events are a theoretical possibility following intravitreal use of vascular endothelial growth factor inhibitors.

Retrospective cohort studies[1-3] found no association between intravitreal ranibizumab and cardiovascular events such as stroke, myocardial infarction, venous thromboembolism, and congestive heart failure. However, an analysis[4] of data pooled from 5 controlled studies in patients with neovascular (wet) age-related macular degeneration showed trends suggesting an increased risk of cerebrovascular accident in patients given ranibizumab compared with controls. Although the rates of events were small and may have been confounded by other risk factors in this population, the authors concluded that continued monitoring of this risk is warranted.

1. Curtis LH, *et al.* Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol* 2010; 128: 1273–9. Correction. *ibid.*; 1623.
2. Campbell RJ, *et al.* Stroke rates after introduction of vascular endothelial growth factor inhibitors for macular degeneration: a time series analysis. *Ophthalmology* 2012; 119: 1604–8.
3. Campbell RJ, *et al.* Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ* 2012; 345: e4203.
4. Bressler NM, *et al.* Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina* 2012; 32: 1821–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lucentis; *Austral.*: Lucentis; *Austria*: Lucentis; *Belg.*: Lucentis; *Braz.*: Lucentis; *Canad.*: Lucentis; *Chile*: Lucentis; *Cz.*: Lucentis; *Denm.*: Lucentis; *Fr.*: Lucentis; *Ger.*: Lucentis; *Gr.*: Lucentis; *Hong Kong*: Lucentis; *Indon.*: Lucentis; *Irl.*: Lucentis; *Israel*: Lucentis; *Ital.*: Lucentis; *Jpn*: Lucentis; *Malaysia*: Lucentis; *Neth.*: Lucentis; *Norw.*: Lucentis; *NZ*: Lucentis; *Philipp.*: Lucentis; *Pol.*: Lucentis; *Port.*: Lucentis; *Rus.*: Lucentis (Луцентис); *S.Afr.*: Lucentis; *Singapore*: Lucentis; *Spain*: Lucentis; *Swed.*: Lucentis; *Switz.*: Lucentis; *Thai.*: Lucentis; *Turk.*: Lucentis; *UK*: Lucentis; *Ukr.*: Lucentis (Луцентис); *USA*: Lucentis.

Rapeseed Oil

Aceite de nabina o navilla; Aceite de semilla de colza; Colza, aceite de; Colza, huile de; Colza Oil; Olej rzepakowy; Oleum Rapae; Rapae oleum; Rape Oil; Rapsų aliejus; Rapsolja; Repceolaj; Rypsiöljy; Řepkový olej; Рапсовое Масло; Сурепное Масло.
UNII — N4G8379626 (rapeseed oil); K168T6Y0YU (fully hydrogenated rapeseed oil).

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn. USNF* includes fully hydrogenated rapeseed oil and superglycerinated fully hydrogenated rapeseed oil.

Ph. Eur. 8: (Rapeseed Oil, Refined). The fatty oil obtained from the seeds of *Brassica napus* and *Brassica campestris* by mechanical expression or extraction and then refined. A suitable antoxidant may be added. It contains not more than 2% of erucic acid. A clear light yellow liquid. Practically insoluble in water and in alcohol; miscible with petroleum spirit. Store in well-filled airtight containers. Protect from light.

USNF 31: (Fully Hydrogenated Rapeseed Oil). A mixture of triglycerides in which the fatty acid composition is a mixture of saturated fatty acids. It is obtained by refining and hydrogenating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white, waxy solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

USNF 31: (Superglycerinated Fully Hydrogenated Rapeseed Oil). A mixture of mono-, di-, and triglycerides, with triglycerides as a minor component. It is obtained by refining, hydrogenating, and glycerinating oil obtained from the seeds of *Brassica napus* and *Brassica campestris*. It contains not more than 1% of erucic acid. A white solid. Insoluble in water and in alcohol. Store in airtight containers. Protect from light.

Profile

Rapeseed oil has been used in liniments in place of olive oil. It is used in some countries as an edible oil but the erucic acid ($C_{22}H_{42}O_2$=338.6) content of the oil has been implicated in muscle damage. The erucic acid content of oils and fats intended for human consumption and of foodstuffs containing oil or fat is subject to legal control. Contaminated rapeseed oil was the cause of the toxic oil syndrome that affected thousands of Spanish citizens in early 1981; it was associated with rapeseed oil denatured with 2% aniline, although the exact causative agent was never discovered. Refined rapeseed oil with a lower erucic acid content is known as canola oil (see p. 2469.2). Rapeseed oil is also used in industrial manufacturing.

There has been some debate whether the frequency of allergic respiratory symptoms in sensitive individuals is increased in areas in which oilseed rape is cultivated.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Fissan-Pate.

Raspberry Leaf

Frambuesa, hoja de; Rubi Idaei Folium; Малиновый Лист.
UNII — 8O2V33JG64.

Profile

Raspberry leaf consists of the dried leaflets of *Rubus idaeus* (Rosaceae). It contains a principle, readily extracted with hot water, which relaxes the smooth muscle of the uterus and intestine of some *animals*.

Raspberry 'tea' has been a traditional remedy for painful and profuse menstruation and for use before and during labour. The infusion has also been used as an astringent gargle.

References.
1. Simpson M, *et al.* Raspberry leaf in pregnancy: its safety and efficacy in labor. *J Midwifery Womens Health* 2001; **46:** 51–9.
2. Holst L, *et al.* Raspberry leaf—should it be recommended to pregnant women? *Complement Ther Clin Pract* 2009; **15:** 204–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Cramplex; *Cz.*: Detsky Caj s Hermankem; Diabetan; Hypotonicka†; Species Cholagogae Planta†; *Philipp.*: Completia†.

Red Yeast Rice

Red Rice Yeast; Красный Ферментированный Рис.

Profile

Red yeast rice is the product of fermentation of rice with the red yeast *Monascus purpureus*. It has a long history of use in China as a red food colorant and flavour, and has also been used in traditional Chinese medicine. Red yeast rice contains HMG-CoA reductase inhibitors (mainly lovastatin) and is used as a dietary supplement for hyperlipidaemias. There have been some reports of hepatotoxicity and rhabdomyolysis associated with its use.

References
1. Prasad GV, *et al.* Rhabdomyolysis due to red yeast rice (Monascus purpureus) in a renal transplant recipient. *Transplantation* 2002; **74:** 1200–1.
2. Smith DJ, Olive KB. Chinese red rice-induced myopathy. *South Med J* 2003; **96:** 1265–7.
3. Anonymous. *Monascus purpureus* (red yeast rice). *Altern Med Rev* 2004; **9:** 208–10.
4. Liu J, *et al.* Chinese red yeast rice (*Monascus purpureus*) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. *Chin Med* 2006; **1:** 4. Available at: http://www.cmjournal.org/content/pdf/1749-8546-1-4.pdf (accessed 11/05/09)
5. Mueller PS. Symptomatic myopathy due to red yeast rice. *Ann Intern Med* 2006; **145:** 474–5.
6. Roselle H, *et al.* Symptomatic hepatitis associated with the use of herbal red yeast rice. *Ann Intern Med* 2008; **149:** 516–7.
7. Lapi F, *et al.* Myopathies associated with red yeast rice and liquorice: spontaneous reports from the Italian Surveillance System of Natural Health Products. *Br J Clin Pharmacol* 2008; **66:** 572–4.
8. Becker DJ, *et al.* Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. *Ann Intern Med* 2009; **150:** 830–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Monaless; *Fr.*: Arterin; Temperol; *Indon.*: Redaxin†; *Malaysia*: Hypocol; Lipascor; *Singapore*: HypoCol; Lipascor.

Multi-ingredient Preparations. *Fr.*: Arterin Plus.

Relaxin

Relaxina; Релаксин.
CAS — 9002-69-1.

Profile

Relaxin is a polypeptide hormone that has been extracted from the corpus luteum of the ovaries of pregnant sows, although a human recombinant form is also now available. It is reported to be related structurally to insulin and has a molecular weight of about 6000.

Relaxin is secreted by the human corpus luteum during pregnancy and is thought to interact with other reproductive hormones. It acts on connective tissue, including collagen, and causes relaxation of the pubic symphysis and softening of the uterine cervix. In many *animal* species relaxin appears to play a major part in cervical ripening before parturition; significant species difference is shown. It has been studied for cervical ripening in humans. Recombinant human relaxin has also been investigated in infertility, cardiovascular disorders, and scleroderma (p. 1938.3).

References.
1. Seibold JR, *et al.* Safety and pharmacokinetics of recombinant human relaxin in systemic sclerosis. *J Rheumatol* 1998; **25:** 302–7.
2. Seibold JR, *et al.* Recombinant human relaxin in the treatment of scleroderma: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **132:** 871–9.
3. Kelly AJ, *et al.* Relaxin for cervical ripening and induction of labour. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester; John Wiley; 2001 (accessed 28/04/06).

Resveratrol

NSC-327430; Ресвератрол; 3,4′,5-Stilbenetriol; 3,4′,5-Trihydroxystilbene.
(E)-5-[2-(4-Hydroxyphenyl)ethenyl]-1,3-benzenediol.
$C_{14}H_{12}O_3$=228.2
CAS — 501-36-0.
UNII — Q369O8926L.

Profile

Resveratrol is a phytoalexin present in a range of plant sources including species of *Arachis, Pinus, Polygonum, Veratrum,* and *Vitis*. It is thought to be one of the compounds responsible for the cardioprotective action of wine (see Grape, p. 2521.3, and Flavonoid Compounds, p. 2505.2).

Resveratrol used in commercial preparations is often derived from the root of Japanese knotweed, *Fallopia japonica* (*Polygonum cuspidatum*; *Reynoutria japonica*) (Polygonaceae) often as the racemate although the *trans*-isomer is also promoted.

Resveratrol is promoted as an antoxidant for the prevention of atherosclerosis. It also has mixed agonist/antagonist activity at oestrogen receptors and some anti-inflammatory and antiproliferative activity, and is under investigation in the prevention and treatment of malignancy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Ultraselem; *Indon.*: Lecitrol; *Ital.*: Biogel Resv; Linfoflu; Res Vin†; Resvelife Sole; Resvelife; Sametrix; Skinproject; *USA*: Alive Mens Energy; Alive Once Daily Womens 50+ Ultra Potency; Alive Womens 50+; *Venez.*: Uvagen.

Rhamnose

Ramnosa; Ramnoza; L-Rhamnose; Рамноза.
6-Deoxy-L-mannose.
$C_6H_{12}O_5$=164.2
CAS — 3615-41-6.
UNII — QN34XC755A.

Profile

Rhamnose is a monosaccharide used to assess intestinal permeability.

For reference to the use of rhamnose in the differential sugar absorption test, see Diagnosis and Testing under Lactulose, p. 1851.1.

References.
1. van Nieuwenhoven MA, *et al.* The sensitivity of the lactulose/rhamnose gut permeability test. *Eur J Clin Invest* 1999; **29:** 160–5.
2. Haase AM, *et al.* Dual sugar permeability testing in diarrheal disease. *J Pediatr* 2000; **136:** 232–7.
3. van Nieuwenhoven MA, *et al.* Effects of pre- and post-absorptive factors on the lactulose/rhamnose gut permeability test. *Clin Sci* 2000; **98:** 349–53.

Rhatany Root

Krameria; Krameria Root; Ratanhia, racine de; Ratanhiae Radix; Ratanhiagyökér; Ratanhiawurzel; Ratanhový kořen; Ratania, raíz de; Ratanianjuuri; Rataniarot; Ratanijų šaknys; Корень Ратании.
UNII — P29ZH1A35Z.

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

Ph. Eur. 8: (Rhatany Root). The dried, usually fragmented, underground organs of *Krameria triandra*. It contains not less than 5% of tannins, expressed as pyrogallol, calculated with reference to the dried drug. It is known as Peruvian rhatany. Protect from light.

Profile

Rhatany root has astringent properties and is used in herbal preparations for a variety of disorders, including oropharyngeal inflammation.

Homoeopathy

Rhatany root has been used in homoeopathic medicines under the following names: Ratanhia; Krameria triandra; Ratanhiae radix; Ratania peruviana; Ratan.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Parodontax.

Multi-ingredient Preparations. *Arg.*: Esculeol P; Parodontax Fluor; *Austria*: Parodontax†; *Braz.*: Malvatricin Natural Organic†; Parodontax†; *Ger.*: Ratanhia comp†; Repha-Os†; *Switz.*: Kemosan Eau Dentifrice†; Prosal N; Sanogencive.

Homoeopathic Preparations. *Austral.*: Snore Eze; *Austria*: Haemex; *Canad.*: Avenoc†; Hylands Hemorrhoids; *Fr.*: Avenoc; *Port.*: Avenoc; *Rus.*: Paeonia-Plus (Пеония-Плюс); *UK*: Medicinal Gargle.

Pharmacopoeial Preparations
Ph. Eur.: Rhatany Tincture.

Rhus

Sumach Berries; Сумах (*Rhus*); Zumaque.
UNII — RHH784E0K6 (Rhus glabra).

Pharmacopoeias. *Br.* includes Toxicodendron Quercifolium for Homoeopathic Preparations.

BP 2014: (Toxicodendron Quercifolium for Homoeopathic Preparations). Fresh, young, not yet lignified shoots, with leaves, of *Toxicodendron quercifolium*. The shoots contain a yellowish-white milky sap that is a strong cutaneous irritant and darkens the skin. Contact with the skin and mucous membranes is to be avoided.

Profile

Rhus consists of the dried fruits of the smooth or Pennsylvanian sumach, *Rhus glabra* (Anacardiaceae). It has astringent and reputed diuretic properties. *R. aromatica* has been used similarly to *R. glabra*.

Poison ivy (*R. radicans*) and poison oak (*R. toxicodendron*; *Toxicodendron quercifolium*; *T. pubescens*), species growing in the USA, contain irritant poisons, such as urushiol, that produce severe contact dermatitis. Extracts of poison ivy and poison oak have been used for the prophylaxis of poison ivy dermatitis but their efficacy has not been proved. The spice sumac is prepared from the berries of *R. coriaria*.

Homoeopathy

Some *Rhus* spp. have been used in homoeopathic medicines under the following names: Toxicodendron

quercifolium; Rhus toxicodendron; Rhus. tox.; Rhus glabra; Rhus glab; Rhus aromatica; Rhus arom.

References.
1. Gladman AC. *Toxicodendron* dermatitis: poison ivy, oak, and sumac. *Wilderness Environ Med* 2006; 17: 120–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Hernidisc; Joint & Muscle Cream; *Canad.*: Cystoforce†; *Chile*: Rhus Opodeldoc; *Ger.*: Granu Fink Femina; Rhus-Rheuma-Gel N; *S.Afr.*: Zeel; Zeel.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Arthritis Relief; Childrens Cold and Flu Relief; Echine†; Homoderma; Joint & Muscle Oral Spray†; Sports Ice Joint & Muscle; *Austria*: Apozema Allium Cepa compositum; Apozema Apis compositum; Echinacea-Cosmoplex; Globuli gegen Hautausschlage; Ledum Med Complex; Rheuma; Rhus Med Complex; Wirbelsaule- und Gelenkstropfen Nr 2†; *Canad.*: Arnica-Heel Comp†; Arthritis Pain Formula; Bed Wetting†; Bioactiv E†; Bladder Irritation; Calnor†; Capsicum + Arthri-Cream; Echinacea Compositum; EnurAid; Fibromyalgie; Herpes Soothing Cream; Hyalgesic LBP†; Hylagesic APF; Hylands Formula E; Hylands Kinder-BW; Hylands LCQ; Hylands Leg Cramps; Ivernax; Leg Cramps with Quinine; Poison Ivy/Oak; Rudistrol†; SK Complex†; Zeel Comp; *Chile*: Apis Compuesto; Arnica Compuesta; Bioactiv E; *Cz.*: Gelsemium-Homaccord; Zeel Compositum; Zeel Salbe†; *Fr.*: Abbe Chaupitre no 1†; Abbe Chaupitre no 23†; Abbe Chaupitre no 25†; Abbe Chaupitre no 59†; Abbe Chaupitre no 6; Abbe Chaupitre no 82†; Arthro-Drainol; Boripharm No 1†; Boripharm No 22†; Boripharm No 23; Euphorbium Complexe No 88; Gelsemium Complexe No 70; Homeogene 41†; Hypericum Complexe No 26; Rhus Toxicodendron Complexe No 80; Rhus Toxicodendron Compose; Rudistrol†; *Ger.*: Alho-Arthrosan N; Araniforce arthro; Arthrorell N; Bomarthros Harpagophytum Complex; Bryorheum N; Cefadolor Arnica Komplex†; Dularell N; Entzundungstropfen; Gelsemium Comp; Gelsemium Comp; Gnaphalium Injektopas SL; Herpes-Gastreu R68; Hewerheum N†; Infi-Symphytum; Intercostal-Gastreu; Lumbago-Gastreu S R11; Lymphaden Complex; Lymphaden; Mato; Neuri-cyl N Ho-Len-Complex; Pyrogenium; Regenaplex Haut G; rheumaloges; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheuma-Pasc; Rheumaselect; Rheumeda; Rhus toxicodendron N Oligoplex; Rhustoxicorell; Ruta-Gastreu N R55; Schwoneural N; Trauma SL; Traumakatt; Vertizin; Zeel comp; *Hung.*: Gelsemium-Homaccord; Zeel; *Neth.*: Amilite; Artifleur; Bronchillte; Dulcarhus-Gastreu R11; Entero-Gastreu R4; Enulite; Head Care; Homeocare Exercito; Muscle Care; Prurilite; Red Skin; Restructa H; Rhumeel; Rudistrol†; Skin Care; Spiroflor; Spiroflor; Strain care; Zeel comp N; *Rus.*: Briacon (Бриакон); Psorilom (Псорилом); Rewma-Gel (Ревма-Гель); Rhus-Plus (Рус-Плюс); Zeel T (Цель Т); *Switz.*: Lithiumeel; Nelsons Traumatica†; Omida Gel Antirhumatismal; Regenaplex Nr. 31a; Rheuma-Heel; *UK*: Rheumatica; *Ukr.*: Reuma-Gel (Ревма-Гель); *USA*: Preferred Remedies Aches & Pains; Preferred Remedies Fatigue.

Ribonuclease

Ribonucleasa; RNase; Рибонуклеаза.
CAS — 9001-99-4.

Profile

Ribonuclease is an enzyme present in most mammalian tissue, and it is involved in the catalytic cleavage of ribonucleic acid. It has been applied, alone or with other drugs, for its supposed anti-inflammatory properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Cro 50.

Multi-ingredient Preparations. *Mex.*: Ofzim; Ridasa.

Ribonucleic Acid

ARN; Plant Nucleic Acid; Ribonucleico, ácido; Ribose Nucleic Acid; RNA; Yeast Nucleic Acid; Рибонуклеиновая Кислота.

Profile

Ribonucleic acid (RNA) is a nucleic acid (p. 2573.1) in which the pentose sugar moiety of the nucleotides is ribose, the purine bases are adenine (p. 2430.2) and guanine, and the pyrimidine bases are cytosine and uracil (p. 2637.3). RNA exists as a single polynucleotide strand that replicates using DNA as a template during which process the pairing of bases between the complementary strands of RNA and DNA is always the same: adenine with uracil and cytosine with guanine. RNA is present in cell nuclei and cytoplasm and is directly involved in protein synthesis; it also plays a part in encoding genetic information. RNA also carries the genetic material of RNA viruses. Gene suppression by RNA interference (RNAi), using specific double-stranded ribonucleic acid sequences, is under investigation. For the role of RNA as a tool in gene therapy, see p. 2511.2.

Proprietary preparations containing RNA are marketed in some countries for a variety of asthenic and convalescent conditions. RNA has also been tried in the treatment of mental retardation and to improve memory in senile dementia. It may also have a role in enteral feeds under some circumstances.

Immune RNA (extracted from the spleens and lymph nodes of immunised animals) has been tried in the immunotherapy of hepatitis and cancer.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: AU 4 Regeneresen†; Osteochondrin S†; Regeneresen†; RN13 Regeneresen†; *Ukr.*: Nucleinas (Нуклеинат).

Multi-ingredient Preparations. *Arg.*: RNA DNA; *India*: Placentrex; *Spain*: Dertrase; Nucleserina; Policolinosil.

Ribwort Plantain

Heinäratamonlehti; Jitrocelový list; Liść babki lancetowatej; Plantaginis Folium; Plantaginis Lanceolatae; Plantaginis Lanceolatae Folium; Plantain Herb; Plantain lancéolé; Siauralapių gysločių lapai; Spitzwegerich; Spitzwegerichblätter; Spitzwegerichkraut; Svartkämparblad.
ATC Herb — HD02WX5004 (Plantago lanceolata: *herb*); *HR05YA5018* (Plantago lanceolata: *herb*); *HA01WB5004* (Plantago lanceolata: *leaf*).
UNII — 2YWL9J7EE8.

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

Ph. Eur. 8: (Ribwort Plantain; Plantaginis Lanceolatae Folium). The whole or fragmented, dried leaf and scape of *Plantago lanceolata*. It contains not less than 1.5% of total *ortho*-dihydroxycinnamic acid derivatives expressed as acteoside ($C_{29}H_{36}O_{15}$ = 624.6) with reference to the dried drug. Protect from light.

Profile

Ribwort plantain is an ingredient in herbal remedies used for catarrh and inflammation of the upper respiratory tract. Plantain (*P. major*, *P. asiatica*, or *P. depressa*) is described on p. 2592.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Jitrocelovy; *Fr.*: Sensivision au plantain; *Ger.*: Broncho-Sem; Tetesept Husten Saft; Tetesept Husten Tropfen; *Pol.*: Lancetan; Lanceticum; Plantagen.

Multi-ingredient Preparations. *Austria*: Brust- und Hustentee St Severin; Grippetee St Severin; Pneumopan†; Scottopect; *Canad.*: Honey Herb Cough Drops†; Original Herb Cough Drops†; *Cz.*: Biotussil; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Mucoplant Jitrocelovy; Pruduskova; Pulmoran; Species Pectorales Planta; Thymomel; *Ger.*: Equisil N†; Kneipp Husten- und Bronchial-Tee†; *Hung.*: Gombarex; *Pol.*: Babicum; Bronchial†; Echinasal; Flegatussin†; Gwajatussin; Padma 28; Pectobonisol; Plantifort; Saponarex; *Rus.*: Eucabal (Эвкабал); Herbion Plantain Syrup (Гербион Сироп Подорожника); Stoptussin-Fito (Стоптуссин-фито); *Switz.*: Arteria-vita; Nican†; Pastilles bronchiques S; Siropectan; Wala Baume pectoral au plantain; Wala Pulmonium suc contre la toux; *UK*: Padma Circosan; *Ukr.*: Eucabal Syrup (Эвкабал Сироп); Herbion Plantaginis Syrup (Гербион Сироп Подорожника); Tussavit (Тусавит).

Ricin

Ricino.
CAS — 9009-86-3.

NOTE. The title ricin is used for the castor seed in *Chin.* and *Fr.*

Profile

Ricin is a lectin present in castor seeds, the seeds of *Ricinus communis* (Euphorbiaceae). It is extremely toxic when given parenterally and the fatal dose by injection has been reported to be around 1 microgram/kg. The toxicity of orally ingested beans depends on how thoroughly they are chewed since the hard seed coat prevents absorption. Ingestion of as few as 3 castor seeds by a child and 4 by an adult may be fatal. Ricin may also be absorbed through abraded skin. It has potential use in aerosol form as an agent of chemical warfare. Toxic effects may be delayed for several days after exposure by any route. Early symptoms include severe gastrointestinal irritation, haemorrhage, vomiting, and diarrhoea, which may result in circulatory collapse. Abnormal liver function tests and pulmonary oedema have been reported. Ophthalmological disturbances ranging from irritation and conjunctivitis to optic nerve damage may occur; miosis and mydriasis have also been reported. Proteinuria, haematuria, and renal impairment may develop and serum creatinine levels may be raised. In severe cases haemolysis of the red blood cells with subsequent acute renal failure may occur. Fatalities due to multi-organ failure have occurred. If the patient presents within 1 hour of ingestion any seeds may be removed by gastric lavage and activated charcoal given. Treatment thereafter is symptomatic.

After expression of the oil from castor seeds (see p. 2472.1), the ricin remaining in the seed cake or 'pomace' is destroyed by steam treatment. The detoxified pomace is used as a fertiliser.

Ricin conjugated with monoclonal or polyclonal antibodies is being studied in the treatment of cancers; zolimomab aritox is an example of such a conjugate. Some of these conjugates have been investigated for various malignancies, particularly leukaemias and lymphomas.

Toxicity. A report of ricin toxicity after partial chewing and ingestion of 10 to 15 castor oil seeds,[1] and reviews[2-4] of ricin toxicity, including its potential as an agent of chemical warfare.

1. Aplin PJ, Eliseo T. Ingestion of castor oil plant seeds. *Med J Aust* 1997; 167: 260–1.
2. Bradberry SM, *et al.* Ricin poisoning. *Toxicol Rev* 2003; 22: 65–70.
3. Lord MJ, *et al.* Ricin: mechanisms of cytotoxicity. *Toxicol Rev* 2003; 22: 53–64.
4. Audi J, *et al.* Ricin poisoning: a comprehensive review. *JAMA* 2005; 294: 2342–51.

Uses. References to the use of ricin conjugates with monoclonal antibodies in the treatment of cancer.

1. Byers VS, *et al.* Phase I study of monoclonal antibody-ricin A chain immunotoxin XomaZyme-791 in patients with metastatic colon cancer. *Cancer Res* 1989; 49: 6153–60.
2. Oratz R, *et al.* Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (XMMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: results of a phase II trial. *J Biol Response Mod* 1990; 9: 345–54.
3. Anonymous. Application considered for immunotoxin in treatment of graft-vs-host disease. *JAMA* 1991; 265: 2041–2.
4. Amlot PL, *et al.* A phase I study of an anti-CD22-deglycosylated ricin A chain immunotoxin in the treatment of B-cell lymphomas resistant to conventional therapy. *Blood* 1993; 82: 2624–33.
5. Senderowicz AM, *et al.* Complete sustained response of a refractory, post-transplantation, large B-cell lymphoma to an anti-CD22 immunotoxin. *Ann Intern Med* 1997; 126: 882–5.
6. Multani PS, *et al.* Phase II clinical trial of bolus infusion anti-B4 blocked ricin immunoconjugate in patients with relapsed B-cell non-Hodgkin's lymphoma. *Clin Cancer Res* 1998; 4: 2599–2604.
7. Dinndorf P, *et al.* Phase I trial of anti-B4-blocked ricin in pediatric patients with leukemia and lymphoma. *J Immunother* 2001; 24: 511–16.
8. Schnell R, *et al.* Clinical evaluation of ricin A-chain immunotoxins in patients with Hodgkin's lymphoma. *Ann Oncol* 2003; 14: 729–36.
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Ricinoleic Acid

Kwas rycynolowy; Ricinoleico, ácido; Рицинолеиновая Кислота.
CAS — 141-22-0.
UNII — I2D0F69854.

Profile

Ricinoleic acid is a mixture of fatty acids obtained by the hydrolysis of castor oil. It is an ingredient of some proprietary vaginal jellies used to maintain or restore normal vaginal acidity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Israel*: Glovan; *USA*: Acid Jelly†.

Rilonacept *(USAN, rINN)*

IL-1 Trap; Interleukin-1 Receptor; Interleukin-1 Trap; Rilonaceptum; Рильонацепт.
CAS — 501081-76-1.
ATC — L04AC04.
ATC Vet — QL04AC04.
UNII — 8K80YB5GMG.

Uses and Administration

Rilonacept is an interleukin-1 blocker used in the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders. Rilonacept is a soluble decoy interleukin-1 receptor that binds interleukin-1β (p. 2533.3) and blocks its actions at cell surfaces.

Rilonacept is given by subcutaneous injection. The solution, when prepared according to the manufacturer's

directions, contains 160 mg per 2 mL and this is the maximum amount that should be given as a single injection or at a single site; if a larger dose is required (as at loading) two separate injections should be given on the same day at two different sites.

The loading dose is 320 mg (as two separate injections). A single injection of 160 mg is then given once weekly. The loading dose for children aged 12 to 17 years is 4.4 mg/kg up to a maximum of 320 mg (given as one or two injections with a maximum single-injection volume of 2 mL). A single injection of 2.2 mg/kg up to a maximum of 160 mg is then given once weekly.

Rilonacept is also under investigation for the treatment of gout.

References.
1. Goldbach-Mansky R, *et al.* A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum* 2008; **58**: 2432–42.
2. Hoffman HM, *et al.* Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008; **58**: 2443–52.
3. Terkeltaub R, *et al.* The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann Rheum Dis* 2009; **68**: 1613–17.

Administration in children. For doses in children aged 12 to 17 years, see p. 2604.3.

Adverse Effects and Precautions

The adverse effects that have been reported most commonly with rilonacept are injection site reactions, headache, sinusitis, and respiratory-tract infections.

Rilonacept has been associated with an increased incidence of serious infections and it should therefore not be given to patients with active or chronic infections. It should be given with caution to patients with a history of recurring infections, or underlying conditions that may predispose them to developing infections. Rilonacept treatment should be stopped in patients who develop severe infections. Patients should be screened for active and latent tuberculosis infection before starting rilonacept treatment. Patients should be up to date with appropriate immunisation schedules, including pneumococcal vaccine and inactivated influenza, before starting treatment with rilonacept. Live vaccines should not be given at the same time as rilonacept unless the benefits clearly outweigh the risks. Giving other interleukin-1 inhibitors or tumour necrosis factor inhibitors at the same time as rilonacept may increase the risk of serious infections. Treatment with immunosuppressants at the same time as rilonacept could theoretically increase the risk of malignancies.

Treatment with rilonacept should not be started in patients with neutropenia, and it is recommended that neutrophil counts should be taken before starting treatment, 1 to 2 months later, and periodically thereafter. Lipid profiles should be monitored in patients taking rilonacept for the treatment of CAPS.

Development of antibodies directed against the receptor domains of rilonacept have been detected in 35% of patients, although it is not clear what effect this might have on efficacy or safety.

Vertigo has been reported with rilonacept treatment, and patients should be advised to avoid driving or operating machinery if this occurs.

Interactions

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-1, and cytochrome P450 expression may therefore be normalised when treatment with an interleukin-1 inhibitor such as rilonacept is started. This becomes clinically significant for cytochrome P450 isoenzyme substrates that have narrow therapeutic ratios where the dose has to be individually adjusted (e.g. warfarin). Therefore when starting or stopping therapy with rilonacept, patients being treated with such drugs should be monitored as doses of these drugs may need to be adjusted.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Rilonacept Regeneron†; *USA*: Arcalyst.

Riluzole *(BAN, USAN, rINN)*

PK-26124; Rilutsoli; Riluzol; Riluzolum; RP-54274; Рилузол.
2-Amino-6-(trifluoromethoxy) benzothiazole; 6-Trifluoromethoxy-1,3-benzothiazol-2-ylamine.
$C_8H_5F_3N_2OS$=234.2
CAS — 1744-22-5.
ATC — N07XX02.
ATC Vet — QN07XX02.
UNII — 7LJ087RS6F.

Pharmacopoeias. In *US*.

USP 36: (Riluzole). A white to slightly yellow powder or crystalline powder. Very slightly soluble in water; freely soluble in alcohol, in acetonitrile, and in dichloromethane; slightly soluble in hexane.

Uses and Administration

Riluzole is a glutamate antagonist used in the management of amyotrophic lateral sclerosis, a form of motor neurone disease. Riluzole is indicated to slow progression of early disease but efficacy has not been shown in its late stages. The precise mechanism of action is unknown but it may inhibit presynaptic glutamate release and interfere with its postsynaptic effects. The usual adult dose of riluzole is 50 mg twice daily given orally on an empty stomach.

Motor neurone disease. Motor neurone disease (motoneuron disease) represents a group of fatal progressive degenerative disorders that affect upper and/or lower motor neurones in the brain and spinal cord. The most common form of motor neurone disease is amyotrophic lateral sclerosis (known in the USA as Lou Gehrig's disease), which involves both upper and lower motor neurones. It produces muscular atrophy and weakness and symptoms of progressive bulbar palsy such as slowness of movement and speech disturbances. Most patients die within 2 to 5 years of disease onset, usually from respiratory failure. There is no completely effective treatment and management remains largely supportive with appropriate symptomatic management of spasticity (p. 2014.2), pain (p. 10.1), and sialorrhoea. Tricyclic antidepressants are widely used for their multiple beneficial effects. Occupational and speech therapy also play a crucial role in maximising function. Pathological crying or laughing (pseudobulbar affect) may occur in as many as 50% of patients and has been treated with amitriptyline or fluvoxamine. Dysphagia may eventually compromise food and fluid intake necessitating enteral nutrition as an alternative or supplemental route for oral nutrition. Respiratory support will ultimately be necessary, initially with non-invasive ventilation but progressing eventually to tracheostomy.

Although the pathogenesis of motor neurone disease is still uncertain, it is thought that accumulation of the excitatory neurotransmitter glutamate in the CNS may be involved. Clinical studies have shown riluzole, a glutamate antagonist, to be modestly effective in prolonging survival by an average of 3 months and delaying the time to use of tracheostomy. However, there are still insufficient data to be able to assess which patients would derive greatest benefit. Additionally, questions have been raised about the clinical usefulness of riluzole in terms of cost-benefit, and there are concerns about adverse effects, notably hepatotoxicity.

Also under study for the treatment of motor neurone disease are somatomedins, in particular mecasermin (insulin-like growth factor I). Neurotrophic factors have been investigated including brain-derived neurotrophic factor (BDNF) and recombinant ciliary neurotrophic factor (CNTF), but results have been generally inconclusive. Glial-cell-derived neurotrophic factor (GDNF) and xaliproden are under investigation.

There has been some interest in the antiepileptic drug gabapentin, which may inhibit glutamate formation in the CNS from branched-chain amino acids. Lamotrigine and topiramate have also been tried but with disappointing results. ONO-2506 is an enantiomeric homologue of valproate that is also under investigation. Dextromethorphan has been studied in amyotrophic lateral sclerosis. Minocycline has shown neuroprotective effects in *animal* studies and is therefore also being studied in this condition; ceftriaxone is also under investigation. Immunoglobulins have been tried in some forms of motor neurone disease such as multifocal motor neuropathy.

Antoxidants, including vitamins C and E, are commonly used by patients in the belief that one mechanism for neuronal death is free radical accumulation resulting from oxidative stress. However, despite substantial literature on the subject and widespread use of antoxidants, significant evidence to support their benefit in motor neurone disease is lacking. Creatine supplements have been tried in a bid to preserve motor function and motor neurones, although benefit has not been shown in controlled studies.

A small percentage of patients with familial amyotrophic lateral sclerosis has been shown to have a mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase but there has been no consensus as to whether patients with this mutation should be given superoxide dismutase supplements.

References.
1. Ludolph AC, Riepe MW. Do the benefits of currently available treatments justify early diagnosis and treatment of amyotrophic lateral sclerosis? — Arguments against. *Neurology* 1999; **53** (suppl 5): S46–S49.
2. Cashman NR. Do the benefits of currently available treatments justify early diagnosis and announcement? — Arguments for. *Neurology* 1999; **53** (suppl 5): S50–S52.
3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344**: 1688–1700.
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7. Choudry RB, Cudkowicz ME. Clinical trials in amyotrophic lateral sclerosis: the tenuous past and the promising future. *J Clin Pharmacol* 2005; **45**: 1334–44.
8. Traynor BJ, *et al.* Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67**: 20–7.
9. Miller RG, *et al.* Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
10. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis or motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
11. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet* 2007; **369**: 2031–41.
12. Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: prepare for the worst and hope for the best. *JAMA* 2007; **298**: 207–16.
13. McDermott CJ, Shaw PJ. Diagnosis and management of motor neurone disease. *BMJ* 2008; **336**: 658–62.
14. Corcia P, Meininger V. Management of amyotrophic lateral sclerosis. *Drugs* 2008; **68**: 1037–48.
15. Miller RG, *et al.* The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; **73**: 1218–26.
16. Miller RG, *et al.* The care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; **73**: 1227–33.

Movement disorders. Beneficial results have been obtained with riluzole in small studies of patients with Huntington's chorea.[1,2] Riluzole has been tried in a small number of patients with early Parkinson's disease but no evidence of benefit was seen.[3] It has also been tried in levodopa-induced dyskinesias in advanced Parkinson's disease with conflicting reports of benefit[4] or no benefit.[5] Riluzole has shown promise as potential symptomatic therapy for cerebellar ataxia in an 8-week study in a small number of patients.[6]

1. Rosas HD, *et al.* Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999; **14**: 326–30.
2. Huntington Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. *Neurology* 2003; **61**: 1551–6.
3. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8**: 271–6.
4. Merims D, *et al.* Riluzole for levodopa-induced dyskinesias in advanced Parkinson's disease. *Lancet* 1999; **353**: 1764–5.
5. Braz CA, *et al.* Effect of riluzole on dyskinesia and duration of the ON state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* 2004; **27**: 25–9.
6. Ristori G, *et al.* Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. *Neurology* 2010; **74**: 839–45.

Psychiatric disorders. Glutamate is implicated in the aetiology of various psychiatric disorders and consequently riluzole has been suggested as a potential treatment in view of its glutamate-modulating properties.

Reviews.
1. Pittenger C, *et al.* Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs* 2008; **22**: 761–86.
2. Zarate CA, Manji HK. Riluzole in psychiatry: a systematic review of the literature. *Expert Opin Drug Metab Toxicol* 2008; **4**: 1223–34.

Adverse Effects and Treatment

Adverse effects associated most commonly with riluzole are asthenia, nausea, elevations in liver enzyme values, headache, and abdominal pain. Other gastrointestinal effects may include diarrhoea or constipation, anorexia, and vomiting. There may be tachycardia, dizziness, vertigo, or somnolence. Circumoral paraesthesia and rhinitis may occur. Lung function may be decreased and cases of interstitial lung disease, sometimes severe, have been reported. Anaphylactoid reactions, angioedema, pancreatitis, and neutropenia have all been reported rarely.

Effects on the blood. Severe neutropenia has been reported[1] in a 71-year old patient with amyotrophic lateral sclerosis receiving standard doses of riluzole. The neutrophil count returned to normal on cessation of riluzole.

See also under Overdosage, p. 2606.1.

1. Weber G, Blitterman H. Riluzole-induced neutropenia. *Neurology* 2004; **62**: 1648.

Effects on the kidneys. A 44-year-old patient developed renal tubular impairment 3 months after starting riluzole

for amyotrophic lateral sclerosis.[1] Tubular function recovered 1 month after stopping riluzole.

1. Poloni TE, *et al.* Renal tubular impairment during riluzole therapy. *Neurology* 1999; **52:** 670.

Effects on the liver. Icteric toxic hepatitis, with jaundice and elevated liver enzyme values, has been reported[1] in an elderly woman receiving riluzole for amyotrophic lateral sclerosis (ALS). Acute hepatitis developed in 2 patients several weeks after starting therapy with riluzole for ALS.[2] Liver histology showed hepatocellular damage with inflammatory infiltration and microvesicular steatosis without fibrosis. Hepatotoxicity was reversed in all these cases when riluzole was stopped.

1. Castells LI, *et al.* Icteric toxic hepatitis associated with riluzole. *Lancet* 1998; **351:** 648.
2. Remy A-I, *et al.* Acute hepatitis after riluzole administration. *J Hepatol* 1999; **30:** 527–30.

Effects on the pancreas. Riluzole was cited[1] as the most likely cause of severe pancreatitis that developed in a 77-year-old woman 6 months after starting therapy for sporadic amyotrophic lateral sclerosis; pancreatic symptoms improved when riluzole was stopped.

1. Drory VE, *et al.* Riluzole-induced pancreatitis. *Neurology* 1999; **52:** 892–3.

Hypersensitivity. A severe life-threatening systemic inflammatory reaction occurred in a patient 2 weeks after starting treatment with riluzole for amyotrophic lateral sclerosis.[1] Symptoms resolved spontaneously on stopping riluzole.

1. Sorenson EJ. An acute, life-threatening, hypersensitivity reaction to riluzole. *Neurology* 2006; **67:** 2260–1.

Overdosage. Severe neutropenia developed in a 63-year-old woman receiving riluzole for amyotrophic lateral sclerosis 10 days after inadvertent dose increase to 200 mg daily (twice the standard recommended dose).[1]

Methaemoglobinaemia has been reported[2] in a 43-year-old patient with amyotrophic lateral sclerosis after intentional overdose with 2.8 g of riluzole. The patient was treated with gastric lavage followed by activated charcoal; intravenous methylthioninium chloride successfully reversed the methaemoglobinaemia. However, the patient died of respiratory failure related to her underlying disease 7 days after the overdose.

An amnesic syndrome that persisted for over a year developed in a woman 4 days after ingestion of 3 g of riluzole.[3]

1. North WA, *et al.* Reversible granulocytopenia in association with riluzole therapy. *Ann Pharmacother* 2000; **34:** 322–4.
2. Viallon A, *et al.* Methemoglobinemia due to riluzole. *N Engl J Med* 2000; **343:** 665–6.
3. Haaxma CA, *et al.* Delayed amnesic syndrome after riluzole autointoxication in Huntington disease. *Neurology* 2006; **66:** 1123–4.

Precautions

Riluzole is contra-indicated in patients with hepatic disease or markedly raised liver enzyme values. Liver function tests should be performed before and throughout treatment with riluzole. In the UK, riluzole is not recommended in patients with renal impairment although US licensed product information states that the pharmacokinetics are not significantly different in renal impairment. Caution should be exercised in those with a history of liver disorders. Patients or their carers should be told how to recognise signs of neutropenia and should be advised to seek immediate medical attention if symptoms such as fever develop; white blood cell counts should be determined in febrile illness and riluzole stopped if neutropenia occurs. Patients who develop respiratory symptoms such as dyspnoea or dry cough should have chest radiography, and in cases suggestive of interstitial lung disease, riluzole should be discontinued immediately. Riluzole may cause dizziness or vertigo and patients should be warned not to drive or operate machinery if these symptoms occur.

Riluzole has been reported to impair fertility in *animals*.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies riluzole 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)

Pharmacokinetics

Riluzole is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur in 1 to 1½ hours. The rate and extent of absorption are decreased when riluzole is given with a high-fat meal. Riluzole is widely distributed throughout the body and is about 97% bound to plasma proteins. It crosses the blood-brain barrier. Riluzole is extensively metabolised to several metabolites in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and subsequent glucuronidation. Riluzole is excreted mainly in the urine, mainly as glucuronides, with an elimination half-life of about 9 to 15 hours. About 2% is excreted unchanged in the urine. Small amounts are excreted in faeces. There is some evidence that clearance of riluzole is reduced in Japanese patients.

References.

1. Le Liboux A, *et al.* Single- and multiple-dose pharmacokinetics of riluzole in white subjects. *J Clin Pharmacol* 1997; **37:** 820–7.
2. Le Liboux A, *et al.* A comparison of the pharmacokinetics and tolerability of riluzole after repeat dose administration in healthy elderly and young volunteers. *J Clin Pharmacol* 1999; **39:** 480–6.
3. Groeneveld GJ, *et al.* Riluzole serum concentrations in patients with ALS: associations with side effects and symptoms. *Neurology* 2003; **61:** 1141–3.
4. van Kan HJ, *et al.* Association between CYP1A2 activity and riluzole clearance in patients with amyotrophic lateral sclerosis. *Br J Clin Pharmacol* 2005; **59:** 310–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rilasat; Rilutek; Rizol; *Austral.*: Rilutek; *Austria*: Rilutek; *Belg.*: Rilutek; *Braz.*: Rilutek; *Canad.*: Rilutek; *Chile*: Rilutek; *China*: Rilutek; Xie Yi Li (协一力); *Cz.*: Rilutek; Sclefic; *Denm.*: Lizolorol†; Rilutek; *Fin.*: Rilutek; *Fr.*: Rilutek; *Ger.*: Rilutek; *Gr.*: Rilutek; *Hong Kong*: Rilutek; *Hung.*: Rilutek; *Irl.*: Rilutek; *Israel*: Rilutek; *Ital.*: Rilutek; *Jpn*: Rilutek; *Mex.*: Rilutek; *Neth.*: Glentek; Lizorolol; Rilutek; *Norw.*: Rilutek; *NZ*: Rilutek; *Pol.*: Rilutek; *Port.*: Rilutek; *S.Afr.*: Rilutek†; *Singapore*: Rilutek; *Spain*: Rilutek; *Swed.*: Rilutek; *Switz.*: Rilutek; *Thai.*: Rilutek; *Turk.*: Rilutek; *UK*: Rilutek; *Ukr.*: Borizol (Боризол); Rilutek (Рилутек); *USA*: Rilutek; *Venez.*: Rilutek.

Pharmacopoeial Preparations
USP 36: Riluzole Tablets.

Rimonabant *(USAN, rINN)*

Rimocaban; Rimonabantum; SR-141716; Римонабант.
5-(*p*-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide.
$C_{22}H_{21}Cl_3N_4O$=463.8
CAS — 168273-06-1 (rimonabant); 158681-13-1 (rimonabant hydrochloride).
ATC — A08AX01.
ATC Vet — QA08AX01.
UNII — RML78EN3XE.

Profile

Rimonabant is a selective cannabinoid type-1 receptor antagonist that has been used as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²), and also for overweight patients (BMI > 27 kg/m²) who have associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. Oral doses of 20 mg daily before breakfast have been used. However, after concern about psychiatric reactions marketing of rimonabant was withdrawn in Europe in January 2009.

Nausea, anxiety, and dizziness occur commonly with rimonabant. Depressive symptoms have also occurred and rimonabant should not be given to patients with major depression or to those being treated with antidepressants; it is also not recommended in patients with other uncontrolled serious psychiatric disorders. Since rimonabant is metabolised by the liver, caution is advised in patients with moderate hepatic impairment. Licensed product information does not recommend its use in patients with severe hepatic or renal impairment because of lack of data in these patient groups. Plasma concentrations of rimonabant are increased when given with ketoconazole; other CYP3A4 inhibitors might have the same effect.

Rimonabant has also been investigated as an aid for smoking cessation.

The action and potential uses of rimonabant have been reviewed.[1-3] Rimonabant is a selective cannabinoid type-1 receptor antagonist that reduces the overactivity of the endocannabinoid (endogenous cannabinoid) system. Studies of rimonabant *in vitro* and in *animals* have shown that it inhibits the proliferation and maturation of adipocytes, improves lipid and glucose metabolism, and regulates food intake and energy balance.[1,3,4]

Four large multicentre randomised controlled studies have been carried out to examine the effects of rimonabant in obesity (RIO) used with a mildly hypocalorific diet (deficit of about 600 kcal/day),[6-9] and all studies showed that rimonabant was of benefit when given at a dose of 20 mg daily. A significant decrease in body-weight and waist circumference was reported from the RIO-Europe study[6] over 1 year, although results from the RIO-North America study[7] conducted over 2 years were more modest; both studies also showed improvement in cardiovascular risk factors. The RIO-Lipids study[8] examined the effects of rimonabant over 1 year in overweight or obese patients with untreated dyslipidaemias and noted improvement in several metabolic risk factors as well as weight loss. Similar results including improvement in plasma-glucose concentrations (as indicated by glycosylated haemoglobin measurements) were obtained in overweight or obese patients with type 2 diabetes mellitus given rimonabant over 1 year in the RIO-Diabetes study.[9] Meta-analysis[10] and systematic review[11] of the 4 studies in the RIO-programme agreed that rimonabant produced statistically greater weight loss than placebo, although some problems with methodology were noted. Since no follow-up data were reported, no conclusion could be reached about weight regain.[10] Of particular concern was the increase in incidence of psychiatric adverse effects such as depression and anxiety in the treatment group, and postmarketing experience in this respect eventually led to withdrawal of marketing authorisation in the EU because it was considered that the risks outweigh the benefits (see above).[10]

Two cases of atrial fibrillation associated with the use of rimonabant in overweight patients have recently been reported.[12]

Rimonabant has also been studied as an aid to smoking cessation but a systematic review[13] of randomised controlled studies concluded that although rimonabant 20 mg daily may be of benefit in stopping smoking, the evidence in maintaining abstinence is inconclusive.

1. Boyd ST, Premming BA. Rimonabant—a selective CB1 antagonist. *Ann Pharmacother* 2005; **39:** 684–90.
2. Gelfand EV, Cannon CP. Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol* 2006; **47:** 1919–26.
3. Henness S, *et al.* Rimonabant. *Drugs* 2006; **66:** 2109–19.
4. Patel PN, Pathak R. Rimonabant: a novel selective cannabinoid-1 receptor antagonist for treatment of obesity. *Am J Health-Syst Pharm* 2007; **64:** 481–9.
5. Xie S, *et al.* The endocannabinoid system and rimonabant: a new drug with a novel mechanism of action involving cannabinoid CB_1 receptor antagonism — or inverse agonism — as potential obesity treatment and other therapeutic use. *J Clin Pharm Ther* 2007; **32:** 209–31.
6. Van Gaal LF, *et al.* Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005; **365:** 1389–97. Correction. *Ibid.* **366:** 370.
7. Pi-Sunyer FX, *et al.* Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006; **295:** 761–75.
8. Després J-P, *et al.* Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; **353:** 2121–34.
9. Scheen AJ, *et al.* RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006; **368:** 1660–72.
10. Christensen R, *et al.* Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370:** 1706–13.
11. Curioni C, André C. Rimonabant for overweight or obesity. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 14/02/08).
12. Cocco G, Chu D. Rimonabant may induce atrial fibrillation. Abridged version: *BMJ* 2009; **338:** 296. Full version: http://www.bmj.com/cgi/content/full/338/jun12_1/b1061?view=long&pmid=19525304 (accessed 01/10/09)
13. Cahill K, Ussher MH. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 14/02/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acomplia; Resibant; *Austria*: Acomplia†; *Belg.*: Acomplia†; *Cz.*: Acomplia†; Zimulti†; *Denm.*: Acomplia†; *Fr.*: Acomplia†; *Gr.*: Acomplia†; *Hong Kong*: Acomplia†; *Israel*: Acomplia†; *Ital.*: Acomplia†; *Neth.*: Zimulti†; *Norw.*: Acomplia†; *Port.*: Zimulti†; *Russ.*: Zimulti (Зимулти); *Swed.*: Acomplia†; *Switz.*: Acomplia†; *UK*: Acomplia†.

Rociverine *(rINN)*

LG-30158; Rociverina; Rociverine; Rociverinum; Роциверин.
2-Diethylamino-1-methylethyl *cis*-1-hydroxy(bicyclohexyl)-2-carboxylate.
$C_{20}H_{37}NO_3$=339.5
CAS — 53716-44-2.
ATC — A03AA06.
ATC Vet — QA03AA06.
UNII — VI08KS44V0.

Profile

Rociverine is an antispasmodic that has been given orally in doses of 30 to 40 mg or rectally in doses of 50 to 75 mg daily. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Rilaten (里拉通); *Ital.*: Rilaten.

Rose Bengal Sodium

CI Acid Red 94; Colour Index No. 45440; Rosa de bengala sódico; Rose Bengal; Sodium Rose Bengal; бенгальский розовый.

The disodium salt of 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein.

$C_{20}H_2Cl_4I_4Na_2O_5$=1017.6

CAS — 11121-48-5 (rose bengal); 632-69-9 (rose bengal disodium).

ATC — S01JA02.

ATC Vet — QS01JA02.

UNII — 956575SN5L.

NOTE. The name Rose Bengale has been applied to the substance described in this monograph as well as to dichlorotetraiodofluorescein (CI Acid Red 93; Ext. D & C Reds Nos. 5 and 6; Colour Index No. 45435), a compound used as its disodium or dipotassium salt as a colouring agent.

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

Profile

Rose bengal sodium stains devitalised conjunctival and corneal epithelial cells as well as mucus and is used as an aid in the diagnosis of dry eye. It is used to detect or assess ocular damage resulting from Sjögren's syndrome or from ill-fitting contact lenses, and for keratitis, squamous cell carcinomas, and detection of foreign bodies. Rose bengal sodium is applied as 1% eye drops or as sterile papers impregnated with the dye.

Instillation of this dye may be painful, especially in dry eyes. Rose bengal sodium can stain skin, clothing, and soft contact lenses. Rose bengal sodium should not be used before taking swabs as it possesses some antiviral activity.

Rose bengal sodium is taken up by the liver and excreted in the bile; the iodine-131-labelled compound (p. 2226.1) has been used as a diagnostic aid in the determination of hepato-biliary function.

Reviews.

1. Khan-Lim D, Berry M. Still confused about rose bengal? *Curr Eye Res* 2004; 29: 311–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Ak-Rose; *USA*: Rosets†.

Rose Fruit

Brier Fruit; Csipkerózsa áltermés; Cynorrhodon; Cynosbati Fructus; Cynosbati Pseudofructus; Dog Rose Fruits; Églantier; Erškėčių vaisiai; Escaramujo; Escarbaculo; Hips; Hypanthium Rosae; Nypon; Rosae Fructus; Rosae Pseudo-fructus; Rosal montés; Rose Hips; Ruusunmarja; Šípek; Tapaculo; Плод Шиповника.

ATC Herb — HA11WA5004 (Rosa canina: pseudofruit); HR05YA5020 (Rosa canina: pseudofruit); HM01AW5016 (Rosa canina: fruit); HG04BW5029 (Rosa canina: fruit).

UNII — 3TNW8D08V3 (Rosa canina fruit).

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

Ph. Eur. 8: (Dog Rose). The rose hips made up by the receptacle and the remains of the dried sepals of *Rosa canina*, *R. pendulina*, and other *Rosa* spp., with the achenes removed. It contains not less than 0.3% of ascorbic acid, calculated with reference to the dried drug. Protect from light.

Profile

The fruits of various *Rosa* species, in particular the dog rose, *R. canina*, are used as a source of vitamin C (p. 2110.3). Rose fruit is included in herbal preparations for constipation and urinary-tract disorders. It has also been tried in osteoarthritis and rheumatoid arthritis.

Osteoarthritis. An evidence-based report[1] by the Arthritis Research Campaign in the UK considered that rose fruit was safe and possibly effective in improving some of the symptoms associated with osteoarthritis of the knee or hip. Others[2] have also noted benefit. GOPO((2*S*)-1,2-di-*O*-[(9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoyl]-3-*O*-β-D-galactopyranosyl glycerol), a galactolipid isolated from rose fruit, is claimed by one manufacturer to be the active anti-inflammatory agent.

1. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_1101201015433 1.pdf (accessed 16/08/10)
2. Christensen R, *et al.* Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients?—a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2008; 16: 965–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: I-Flex; *Rus.*: Cholemax (Холемакс); Cholos (Холос); Cholosas (Холосас); *UK*: LitoZin; *Ukr.*: Cholosas (Холосас).

Multi-ingredient Preparations. *Arg.*: Vitamina C-Complex; *Austral.*: Bio C; Calporo†; Flavons†; Hair Skin & Nails; Mega C†; Neo C; Super Cal C†; Sustained Release C; Tresos B PluSe; *Austria*: Aktivanad; Amersan; *Canad.*: Floradix Kindervital†; Floradix Tab†; Rose Hips C; *Chile*: Calcio 520; Natursel-C; Propolkit; Reduc-Te; Romox-ARL; *Cz.*: Amersan; Pruduskova; *Fr.*: Hydracur; *Hung.*: Kilo-Nit; *India*: Britesite; Marc Free; Ophthacare; *Ital.*: Angiorex Complex; Cistefi; Gemiol Plus; Golapiol C; Longevital; Nepiros; *Malaysia*: Nat-C†; *Philipp.*: Delrosa; *Pol.*: Cholesol; Diabetofort; Diges-Tonic; Echinasal; Sedomix; Tiliros; *Rus.*: Arfazetin-E (Арфазетин-Э); Bronchicum Husten (Бронхикум Сироп от Кашля)†; Brusniver (Брусниивер); Bvalar (Эвалар); Kliophyt (Клиофит); Phyto Novo-Sed (Фито Ново-Седа); *Singapore*: Nat-C; Silence; *Switz.*: Silence; Tisane contre les refroidissements; *Thai.*: Blackmores Bio C; Blackmores Naturetime Buffered C; Nat C; *UK*: GlucOsamax; Top C; *USA*: Amino-Opti-C; C Factors "1000" Plus; Ester-C Plus Multi-Mineral; Ester-C Plus; *Venez.*: Ro-C-Var.

Rose Oil

Attar of Rose; Esencia de Rosa; Oleum Rosae; Otto of Rose; Rosa, aceite esencial de; Розовое Масло.

UNII — WUB68Y35M7 (rose oil); FF1Y064QVO (Rosa alba flower oil); H32V31VMWY (Rosa centifolia flower oil); 18920M3T13 (Rosa damascena flower oil); B3Y66352HF (Rosa gallica flower oil).

Pharmacopoeias. In *USNF.*

USNF 31: (Rose Oil). A volatile oil distilled with steam from the fresh flowers of *Rosa gallica*, *R. damascena*, *R. alba*, *R. centifolia*, and varieties of these species (Rosaceae). It is a colourless or yellow liquid, having the characteristic odour of rose. At 25 degrees it is a viscous liquid. On gradual cooling, it changes to a translucent, crystalline mass, easily liquefied by warming. Miscible with an equal volume of chloroform. Store in well-filled airtight containers.

Profile

Rose oil is largely employed in perfumery and toilet preparations and has been used as a flavour. It is also used in aromatherapy. It contains citronellol. Hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Estri-Atlas; *Chile*: Cicapost; Estri-Atlas; *India*: Artrex; *Port.*: Cicapost.

Homoeopathic Preparations. *Ger.*: Aurum/Lavandula comp..

Pharmacopoeial Preparations

USNF 31: Stronger Rose Water;

USP 36: Rose Water Ointment.

Rosemary

Romarin; Romarin (rosemary leaf); Roris Marini; Rosmarininlehti (rosemary leaf); Rosmarin; Rosmarinblad (rosemary leaf); Rosmarini folium (rosemary leaf); Rozmarinų lapai (rosemary leaf); Rozmaringlevél (rosemary leaf); Rozmarýnový list (rosemary leaf); Розмарин.

ATC Herb — HP03BX5006 (Rosmarinus officinalis: leaf); HA03AW5052 (Rosmarinus officinalis: leaf); HA05AW5015 (Rosmarinus officinalis: leaf); HG04BW5030 (Rosmarinus officinalis: leaf); HN05CM5024 (Rosmarinus officinalis: leaf); HD03WX5015 (Rosmarinus officinalis: leaf).

UNII — U67X351P9.

NOTE. The name Wild Rosemary has been applied to the unrelated plant, Marsh Tea (p. 2550.1).

Pharmacopoeias. *Eur.* (see p. vii) includes the dried leaf.

Ph. Eur. 8: (Rosemary Leaf; Rosmarini Folium). The whole, dried leaf of *Rosmarinus officinalis*. It contains not less than 1.2% v/w of essential oil and not less than 3% of total hydroxycinnamic derivatives, expressed as rosmarinic acid ($C_{18}H_{16}O_8$ = 360.3) both with reference to the anhydrous drug.

Profile

Rosemary (*Rosmarinus officinalis*, Lamiaceae) has rubefacient and mild analgesic activity when applied topically, and is included in external preparations for rheumatic and circulatory disorders. It is also reported to have carminative, spasmolytic, and diuretic effects and is included in herbal preparations for gastrointestinal, cardiovascular, and urinary-tract disorders.

Rosemary is a source of rosemary oil (below).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Alrinte.

Multi-ingredient Preparations. *Arg.*: Acnetrol; Acnetrol; Albion; Sequals G; *Austral.*: Avena Complex†; Bacopa & Ginkgo Compound; Garlic Allium Complex; LivCo; Vitanox; *Austria*: Euka; *Belg.*: Cynactil; *Canad.*: Optomega; Phyto-Marinex; Salusan†; *Chile*: Rhus Opodeldoc; Romox-ARL; *Fr.*: Aromadetox†; Boldoflorine; Boldoflorine; Boribel Tisane No 7†; Boribel Tisane No 9; Calmiflorine†; Depuratum; Hepato-Solutines†; Hepatoflorine†; Kotor Articulations; Mediflor Contre la Constipation Passagere No 7; Mediflor Digestive No 3; Mediflor Hepatique No 5; Romarene†; Santane F_{10}†; Santane O1; Santane R_4†; *Ger.*: Canephron N; Melissengeist; *Mex.*: Norex; *Mon.*: Romarinex Chrome; Romarinex; *Pol.*: Cardiactiv; Doppelherz Energovital Tonik K; *Rus.*: Canephron N (Канефрон Н); *Spain*: Linimento Naion; Resolutivo Regium†; *Switz.*: Metabol; *UK*: Cystipret; Outlook; *Ukr.*: Canephron N (Канефрон Н); Fitoval Shampoo Anti-Hair Loss (Фитовал шампунь против выпадения волос); Memory Booster (Мемори Бустер); Vitrum Beauty Elite (Витрум Бьюти Элит); *Venez.*: Flocadep.

Homoeopathic Preparations. *Ger.*: Levisticum S; *Rus.*: Dysmenorm (Дисменорм); *Ukr.*: Dysmenorm (Дисменорм.).

Rosemary Oil

Esencia de Romero; Essence de Romarin; Essência de Alecrim; Oleum Roris Marini; Oleum Rosmarini; Romarin, huile essentielle de; Romero, aceite esencial de; Rosmariiniöljy; Rosmarini aetheroleum; Rosmarini Etheroleum; Rosmarinöl; Rosmarinolja; Rozmarinų eterinis aliejus; Rozmaringolaj; Rozmarýnová silice; Розмариновое Масло.

ATC Herb — HA03AW5051 (Rosmarinus officinalis: essential oil); HM02AW5018 (Rosmarinus officinalis: essential oil).

UNII — 8LGU7VM393.

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

Ph. Eur. 8: (Rosemary Oil). The essential oil obtained by steam distillation from the flowering aerial parts of *Rosmarinus officinalis*. It is available as Spanish type rosemary oil and Moroccan and Tunisian type rosemary oil. Spanish type rosemary oil contains 2.0 to 4.5% borneol, 0.5 to 2.5% bornyl acetate, 8.0 to 12.0% camphene, 13.0 to 21.0% camphor, 16.0 to 25.0% cineole, 1.0 to 2.2% *p*-cymene, 2.5 to 5.0% limonene, 1.5 to 5.0% β-myrcene, 18 to 26% α-pinene, 2.0 to 6.0% β-pinene, 1.0 to 3.5% α-terpineol, and 0.7 to 2.5% verbenone. Moroccan and Tunisian type rosemary oil contains 1.5 to 5.0% borneol, 0.1 to 1.5% bornyl acetate, 2.5 to 6.0% camphene, 5.0 to 15.0% camphor, 38.0 to 55.0% cineole, 0.8 to 2.5% *p*-cymene, 1.5 to 4.0% limonene, 1.0 to 2.0% β-myrcene, 9.0 to 14.0% α-pinene, 4.0 to 9.0% β-pinene, 1.0 to 2.6% α-terpineol, and a maximum of 0.4% verbenone.

A clear, mobile, colourless to pale yellow liquid with a characteristic odour. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Rosemary oil is carminative and mildly irritant. It is used in perfumery and as a flavour and has been employed in hair lotions, inhalations, and liniments. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Rosapinol†.

Multi-ingredient Preparations. *Austral.*: Accelerex painEASE; Accelerex painEASE; Bacopa Complex; Bio-Oil; Bosisto's Vaporising Ointment†; Buky Bearub; Vicks Baby Balsam; *Austria*: Berggeist; Carl Baders Divinal; Opino; Rheuma; Rowalind; *Belg.*: Perubore†; Pulmex Baby; Pulmex†; *Braz.*: Aliviol; Benegel; Gelflex; Nevrol†; *Canad.*: Restorativ Glucosamine Muscle and Joint; *Chile*: Agua del Carmen; Agua Melisa Carminativa; Lefkaflam; *Cz.*: Thrombocid; *Fr.*: Aromadetox†; Aromadigest†; Aromasol; Esculape†; Maghora†; Olioseptil Nez-Gorge; Perubore; Veino Gomenol; *Ger.*: Cor-Vel; Dolo-cyl†; Hingfong-Essenz Hofmanns; polio-elan†; Poly-elan; Retterspitz Ausserlich; Retterspitz Quick Muskel; Rheuma Bad†; Rheuma- und Schmerzsalbe; Thrombocid; Weleda Bronchialbalsam; Weleda-Rheumasalbe M†; *Gr.*: Ilon; Opino; *Hung.*: Inno Rheuma Forte; Inno Rheuma; Inno Rheuma; Pasta Cool; Pulmex Baby; Pulmex; Rosarthron; *Indon.*: Opino†; *Irl.*: Massage Balm with Arnica; *Ital.*: Calyptol; Cinarepa; Neuralta Migren; Valda Propoli†; *Malaysia*: Bio-Oil; *Mon.*: Calyptol; *NZ*: Electric Blue Headlice; Tixylix Chest Rub; Vicks Baby Balsam; *Pol.*: Argol Rheuma; Aromagel†; Aromatol Hot Gel; Depulol; Doppelherz Energovital Tonik†; Pulmex Baby; *Port.*: Thrombocid; *Rus.*: Carmolis Fluid (Кармолис Жидкость); Doppelherz Energotonik (Доппельгерц Энерготоник); Pulmex (Пульмекс)†; Pulmex Baby (Пульмекс Бэби); Theraflu Bro (Терафлю Бро); *S.Afr.*: Arnica

Massage Oil; Balsem Vita GEEL†; Balsem Vita ROOI†; Entressdruppels HM; Oleum Salviae Comp†; Rooilavental; Stuidruppels; *Spain*: Beta Romero; Dolokey†; Masagil†; Tonimax; *Switz.*: DUL-X Cool; DUL-X Sport; DUL-X warm; DUL-X; DUL-X; Echinarom; Nasobol Inhalo; Novital; Perskindol Classic; Perskindol Classic; Pulmex Baby; Pulmex; Pulmex; Spagyrom; Ziegella†; *UK*: Adlantine; Arnica Massage Balm; Medicated Extract of Rosemary; Puncto Rub; Soothol; Tradimed Vapour & Muscle Rub; *Ukr.*: Alflutop (Алфлутоп Гель)†.

Homoeopathic Preparations. *Ger.*: Aconitum Nicotiana comp†; Arnica comp/Apis†; Arnica/Symphytum comp; *UK*: Frost Cream; Rheumadoron.

Roxarsone *(BAN, USAN, rINN)*

NSC-2101; Roxarsona; Roxarsonum; Роксарсон.
4-Hydroxy-3-nitrophenylarsonic acid.
$C_6H_6AsNO_6$=263.0
CAS — 121-19-7.
UNII — H5GU9YQL7L.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Roxarsone). A pale yellow, crystalline powder. Slightly soluble in cold water; soluble in boiling water; freely soluble in dehydrated alcohol, in acetic acid, in acetone, in methyl alcohol, and in alkalis; insoluble in ether and in ethyl acetate; sparingly soluble in dilute mineral acids. It puffs up and deflagrates on heating.

Profile

Roxarsone has been used as a growth promotor in animal feeds.

Royal Jelly

Apilak; Jalea real; Queen Bee Jelly; Маточное Молочко.
CAS — 8031-67-2.
UNII — L497137F0C.

Profile

Royal jelly is a milky-white viscid secretion from the salivary glands of the worker honey bee, *Apis mellifera* (Apidae); it is essential for the development of queen bees. Royal jelly has been used as a nutritional supplement, but of the many and diverse claims made for its therapeutic value, none has been substantiated.

Royal jelly is also included in some cosmetic preparations for its supposed beneficial effect on skin tissue.

Hypersensitivity. For reference to hypersensitivity reactions with bee products, including royal jelly, see under Apis Mellifera, p. 2445.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Apiserum; *Ital.*: Alvear; Biogel; Biovital†; Clinvit; Pa-Real; Rittnogel; Roburvit; Telergon II†; Theogel; Trofomed; *Rus.*: Apilac (Апилак); *UK*: Biobees; Regina Royal One Hundred; Rojema; *Ukr.*: Apilac (Апилак).

Multi-ingredient Preparations. *Arg.*: Energizante Vital con ginseng; Energizante; *Fr.*: Arkoroyal; Aromavital†; Fibromyalgine; Phytozac; *Hung.*: Aktivit; Klimovit; Sam-Ginseng Royal; *Indon.*: Armovit; Hemaviton Energy Drink; Hemaviton Jreng; Neo Hormoviton Greng; Neo Hormoviton; Neo Hormoviton; *Ital.*: Almavigor; Alvear con Ginseng; Apergan; Api Baby; Apiserum con Telergon 1†; Apistress; Bebimix†; Bidro; Bio-200; Biogel Resv; Bioton; Biotrefon Plus; Eavit Plus; Eavit; Eurogel; Fosfarsile Forte†; Fosfarsile Forte; Fosfarsile Junior; Granvit; Longevital; Neoplus; Nerex; Nutrigel; Ottovis; Plusvit; Pollingel; Provitamin A-E; Ribovir; Ristabil; Royal E; Taingel; Vigogel; *Malaysia*: Dermaheal Post Laser Cream; *Mex.*: Hepafol-F; Maxivit; Supravital; *Philipp.*: Jamieson Total Energy; Memovit-E†; Revicon Max; Rogin-E; Vita SL; *Rus.*: Multimax for Eyes (Мультимакс Для Глаз); Prostopine (Простопин); Vitamax (Витамакс)†; *Singapore*: Vitaton; *Spain*: Vitestable; *Thai.*: Multilim RG; *UK*: Regina Royal Concorde; Regina Royal Five; *Ukr.*: Energin (Энергин); Gold Ray (Голд Рей); Rotavit Royal (Ротавит Ройял).

Rubber

Borracha; Caoutchouc; Caucciù; Caucho; Gummi; India-Rubber; Kumi; Каучук.
UNII — 2L0OUUW8IN.

Profile

Rubber consists of the prepared latex of *Hevea brasiliensis* and other species of *Hevea* (Euphorbiaceae). It is used as a component of many medical devices such as catheters, syringes, enema tips, ostomy bags, balloons, and surgical gloves. Hypersensitivity reactions have occurred after direct contact of skin and mucous membranes with rubber components of such products and also after indirect contact with preparations stored in or given by them; deaths have been reported. Reactions have been attributed either to protein components of the rubber or to additives such as preservatives or vulcanisation accelerators. For references to glove starch powder as a possible risk factor in the development of rubber latex allergy, see Glove Powder under Adverse Effects of Starch, p. 2096.2. Cross-sensitivity between rubber proteins and those of certain fruits, including bananas and chestnuts, has been reported.

References.

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Rubidium Iodide

Rubidio, ioduro de; Yoduro de rubidio; Рубидия Йодид.
RbI=212.4
CAS — 7790-29-6.
UNII — 18CYW0VL2X.

Profile

Rubidium iodide has the actions of iodine and the iodides (see p. 2336.3). It is an ingredient of several proprietary ophthalmic preparations promoted for the treatment of eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Facovit; Jodo Calcio Vitaminico; Poliljodurato; Rubjovit.

Rue Oil

Oleum Rutae; Ruda, aceite esencial de; Рутовое Масло.
UNII — VDI0O08XRA.

Profile

Rue oil is a volatile oil obtained from rue, *Ruta graveolens* (Rutaceae). Rue oil and infusions of rue were formerly used as antispasmodics and emmenagogues and are reported to have abortifacient properties. Rue is a photosensitiser and the oil is a powerful local irritant.

Homoeopathy

Rue has been used in homoeopathic medicines under the following names: Ruta; Ruta gra.; Ruta grav.; Ruta graveolens.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Aulo Repelente De Piojos; Max Repel; Max Repel; Rep Locion Repelente; *Austral.*: Hernidisc; Joint & Muscle Cream.

Homoeopathic Preparations. *Austral.*: Arthritis Relief; Sports Ice Joint & Muscle; *Austria*: Apozema Apis compositum; Arnica Komplex†; Repisan; Tropfen bei Verletzungen; Wirbelsaule- und Gelenkstropfen Nr 2†; *Canad.*: Aches & Pains; Arnicaid; Bumps and Bruises; Headache & Migraine L77; Rudistrol†; *Fr.*: Arnica Complexe no 1; Calendula Complexe No 89; Homeofortil†; Homeogene 41†; Phapax; Poconeol no 54; Ranunculus Complexe No 79; Rudistrol†; *Ger.*: Cranio-cyl Ho-Len-Complex; Flenin; Gelenk Albin; Inflossan; Rheucostan R; Rheuma-Pasc; Rheumeda; Ruta-Gastreu N R55; Steirocall S†; Symphytum Rowo†; Venokatt; *Neth.*: Gletar; Muscle Care; Rudistrol†; Strain care; *Rus.*: Repisan (Реписан); Ruta-Plus (Рута-Плюс); *Switz.*: Nelsons Traumatica†; Regenaplex Nr. 25c; Regenaplex Nr. 3; *UK*: Strains Cream; *Ukr.*: Homvio-Reuman (Хомвио-Ревмин).

Ruscogenin

Ruscogenina; Ruskojenin; Рускогенин.
(25*R*)-Spirost-5-ene-1β,3β-diol.
$C_{27}H_{42}O_4$=430.6
CAS — 472-11-7.
UNII — BX192R2VUJ.

Profile

Ruscogenin is a sapogenin obtained from butcher's broom, *Ruscus aculeatus* (Liliaceae). It is reported to have anti-inflammatory and antithrombotic actions and has been applied in the local treatment of haemorrhoids as rectal ointment or suppositories. It has also been tried in peripheral vascular disorders.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flebodolor.

Multi-ingredient Preparations. *Arg.*: Miopropan Proctologico; Procto Venart; *Fr.*: Proctolog; *Gr.*: Ibuproct; *Ital.*: Perfluxi Cremagel; Ruscoroid; *Pol.*: Ruskorex; *Port.*: Proctolog; *Singapore*: Proctolog; *Spain*: Abrasone Rectal; Proctolog; Ruscus; Venacol†; *Turk.*: Proctolog; Progtolog.

Sacrosidase *(USAN)*

EC 3.2.1.26; β-Fructofuranosidase; Glucosucrase; Invertase; Saccharase; Sacrosidasa; Сакрозидаза.
β-D-Fructofuranoside fructohydrolase.
CAS — 85897-35-4.
ATC — A16AB06.
ATC Vet — QA16AB06.
UNII — 8A7F670F2Y.

Profile

Sacrosidase is a therapeutic enzyme used for sucrase replacement therapy in congenital sucrase-isomaltase deficiency. It is given with each meal or snack in usual doses of 8 500 international units for patients up to 15 kg, or 17 000 international units for patients over 15 kg.

Sacrosidase may cause hypersensitivity reactions. The commercial product may contain yeast, yeast products, glycerol, and papain and is contra-indicated in patients known to be hypersensitive to these substances.

References.

1. Treem WR, *et al.* Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999; **28**: 137–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Sucraid.

Multi-ingredient Preparations. *Canad.*: Synergy Defense.

Sage

Feuilles de Sauge; Hármaslevelű zsálya levél (sage leaf, three-lobed); Krūminių šalavijų lapai (sage leaf, three-lobed); List šalvěje lékařské (sage leaf); List šalvěje trojlaločné (sage leaf, three-lobed); Liść szałwii (sage leaf); Orvosi zsálya levél (sage leaf); Salbeiblätter; Salvia; Salviablad (sage leaf); Salviablad, treflikat (sage leaf, three-lobed); Salviae Folium (sage leaf); Salviae Officinalis Folium (sage leaf); Salviae trilobae folium (sage leaf, three-lobed); Salvianlehti, kolmiliuskainen (sage leaf, three-lobed); Salvianlehti (sage leaf); Sauge officinale, feuille de (sage leaf); Sauge trilobée, feuille de (sage leaf, three-lobed); Vaistinių šalavijų lapai (sage leaf); Шалфей.
ATC Herb — HD11AA5001 (Salvia officinalis leaf); HA01WC5004 (Salvia officinalis leaf).
UNII — M9C36LC10E (Salvia officinalis); 065CSD07J (Salvia officinalis leaf); 48JC5720FN (Salvia officinalis flowering top); 236OY0A1BL (Salvia officinalis root).

NOTE. The term Red Sage has been used for both *Salvia officinalis* and *Salvia miltiorrhiza* (Danshen, p. 2491.3).

Pharmacopoeias. *Eur.* (see p. vii) includes separate monographs for the leaf of the common or garden sage (*Salvia officinalis*) and the leaf of Greek or three-lobed sage (*Salvia fruticosa*).

Ph. Eur. 8: (Sage Leaf (Salvia officinalis); Salviae Officinalis Folium). The whole or cut dried leaves of *Salvia officinalis*. The whole drug contains not less than 1.5% v/w and the cut drug not less than 1.0% v/w of essential oil, both calculated with reference to the anhydrous drug. Sage leaf oil is rich in thujone. Protect from light.

Ph. Eur. 8: (Sage Leaf, Three-lobed; Salviae Trilobae Folium). The whole or cut, dried leaves of *Salvia* (*S. triloba*). The whole drug contains not less than 1.8% v/w of essential oil, and the cut drug not less than 1.2% v/w of essential oil, both calculated with reference to the anhydrous drug. It has a spicy odour when ground, similar to eucalyptus oil. Protect from light.

Profile

Plants in several genera are commonly referred to as sage but if the term is used without further qualification it is usually understood to mean the common or garden sage (*Salvia officinalis*). Sage leaf has carminative, antispasmodic, antiseptic and astringent properties and is used as a flavour. It is used in preparations for many purposes, including respiratory-tract disorders, gastrointestinal disorders, and in mouthwashes and gargles for disorders of the mouth and throat. The leaf of the Greek or three-lobed sage (*Salvia fruticosa*) is also used in herbal medicine and it is sometimes found as an adulterant of sage.

Sage is the source of sage oil (see below).

Homoeopathy

Sage has been used in homoeopathic medicines under the following names: Salvia; Salvia officinalis; Salvia officinalis e foliis siccatis; Sal. off.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Nosweat; Salvysat†; *Cz.*: Caj ze Salveje; Florsalmin; Nat Salveje Lekarske†; Salvej Lekarske List†; Salvejova Nat; *Ger.*: Aperisan; Salbei Curarina; Salvysat; Sweatosan N†; *Hung.*: Aperisan; *Ital.*: Saugella Dermoliquido; *Norw.*: Nosweat†; *Pol.*: Aperisan; *Rus.*: Salbei (Шалфей); Salvin (Сальвин); *Switz.*: MenoMed; Valverde bucopharynge; *Turk.*: Parodontax; *UK*: Menoforce Sage; Salvian.

Multi-ingredient Preparations. *Arg.*: Acnetrol; Parodontax Fluor; Sigmafem Free; Sigmafem; Sigmaflavon Plus; Tereonsit; *Austral.*: Femi-Nan; Feminine Herbal Complex; Herbal Throat Spray; Olf†; PM Meno-Care; Wild Yam Complex; *Austria*: Cional; Dynexan; Phytovir; *Braz.*: Parodontax†; *Canad.*: Depuratif des Trappistes; Herbanat†; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; *Chile*: Eciclean; *Cz.*: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Herbadent; Pulmoran; Tormentan; *Fr.*: Bolcitol†; Dexsil Peau; Fibromyalgine Fort; Gonaxine; NurAiD; Santane D_3†; Santane F_{10}†; Saugella Antiseptic; Saugella Antiseptic; Saugella Dermoliquide; Saugella HydraSerum; Tisane D'Ars†; Tisane Hepatique de Hoerdt†; *Ger.*: Amara-Tropfen; InfectoGingi; Melissengeist; Parodontal; *Hung.*: Uroherb; *Israel*: Baby Paste + Chamomile†; Kamilotract; *Ital.*: Donalg; Fito Stomygen†; Saugella Attiva; Saugella Dermolatte; Saugella Fitothym; Saugella Salviettine; Saugella Solido ph 3.5; *Neth.*: Bioforce; *Pol.*: Dentosept A; Dentosept; Enterosol; Herbogastrin; Mucosit; Salumin†; Salviasept; Sanofil; Septosan†; Tymsal; *Rus.*: Elecasol (Элекасол); Fitantis (Фитантис); Inhaphytol No 1 (Ингафитол 1); Pectorales Species No 3 (Грудной Сбор 3); Salvarom (Сальварон); Stomatophit (Стоматофит); *S.Afr.*: Amara†; Dynexan; Fragador†; *Singapore*: Nu-Derm Toner; Purifying Gel; Stop Snoring; *Switz.*: A Vogel Spray pour la gorge; Gouttes Amara; Kernosan Eau Dentifrice†; Mucosan†; Parsenn Creme pour herpes; Phytovir; Prosal N; Strath Gouttes pour les muqueuses; Tisane pectorale et antitussive; Wala Echinacea; *UK*: Echinaforce Sore Throat Spray; Red Sage Catarrh Remedy; *Ukr.*: Ambovit (Амбовит); Elecasol (Элекасол); Fitoval Shampoo (Фитовал шампунь); Klimased (Климасед); Sage Extract with Vitamin C Dr Theiss (Экстракт Шалфея с Витамином С Др Тайсс); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Vitokan (Витокан).

Homoeopathic Preparations. *Austria*: Vocara; *Canad.*: Amaratopfen†; *Chile*: Matico Compuesto; *Fr.*: Mercurius Cyanatus Complexe No 43†; Poconeol no 66; *Ger.*: Flenin; *Neth.*: Vinceel H; *Rus.*: Vocara (Вокара); *UK*: Fragador; *Ukr.*: Vocara (Вокара).

Pharmacopoeial Preparations

Ph. Eur.: Sage Tincture.

Sage Oil

Kvapiųjų šalavijų eterinis aliejus (clary sage oil); Muskatellisalviaöljy (clary sage oil); Muskatellsalviaölja (clary sage oil); Salviae sclareae aetheroleum (clary sage oil); Salviae Sclareae Etheroleum (clary sage oil); Sauge sclarée, huile essentielle de (clary sage oil); Silice šalvěje muškátové (clary sage oil); Шалфейное Масло.

CAS — 8016-63-5 (clary sage oil).

ATC Herb — HA01WC5003 (Salvia officinalis: essential oil).

UNII — U27K0H1H2O.

Pharmacopoeias. *Swiss* includes, Salbeiöl (Salviae aetheroleum), oil from the common or garden sage (*Salvia officinalis*). *Eur.* (see p. vii) includes separate monographs for the oil from the clary sage (*Salvia sclarea*) and from Spanish sage (*Salvia lavandulifolia*).

Ph. Eur. 8: (Clary Sage Oil). Colourless to brownish-yellow liquid, usually pale yellow, with a characteristic odour. It is obtained by steam distillation from the fresh or dried flowering stems of *Salvia sclarea*. Store in airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Ph. Eur. 8: (Spanish Sage Oil). A clear, colourless or pale yellow, mobile liquid with a camphor-like odour. It is obtained by steam distillation from the aerial parts of *Salvia lavandulifolia* collected at the flowering stage. Store at a temperature not exceeding 25 degrees.

Profile

Clary sage oil (from *Salvia sclarea*) and Spanish sage oil (from *S. lavandulifolia*) are used in perfumery and aromatherapy. Sage oil from the common or garden sage (*Salvia officinalis*) (see p. 2608.3) is also used in perfumery but it is not recommended for use in aromatherapy because of its skin irritant properties, nor is it recommended for ingestion due to its thujone content.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Chiacaps; *Fr.*: Node G†.

Multi-ingredient Preparations. *Arg.*: Dermomega; *Austral.*: Advanced Menopause Care; *Austria*: Colda; Coldistan; Parodontax†; Piniment; *Ger.*: Salviathymol N; Trauma-cyl†; Varicylum-S†; Weleda Bronchialbalsam; *Hung.*: Carmol; Szent Lukacs; *Indon.*: Transpulmin Balsam; *Ital.*: Venalta; *Philipp.*: Kamillosan M; Transpulmin Balsam†; *Pol.*: Carmolis; Doppelherz Energovital Tonik†; Salviasept; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); Doppelherz Energotonik (Доппельгерц Энерготоник); Parodontocide (Пародонтоцид); *S. Afr.*: Oleum Salviae Comp†; *Switz.*: Bismorectal†; Denosol; Wiewohl†; Ziegella†; *Ukr.*: Phytolysin Plus (Фитолизин Плюс); Sage Extract with Vitamin C Dr Theiss (Экстракт Шалфея с Витамином С Др Тайсс).

Homoeopathic Preparations. *UK*: Medicinal Gargle.

Salicyl Alcohol *(USAN)*

Salicain; Saligenin; Saligenol; Салициловый Спирт.

2-Hydroxybenzyl alcohol.

$C_7H_8O_2$=124.1

CAS — 90-01-7.

UNII — FA1N0842KB.

NOTE. The name salicain has also been used as a proprietary name for hydroxytetracaine.

Profile

Salicyl alcohol is reported to have local anaesthetic and analgesic properties and has been used in various topical preparations. It is present in the bark of some trees and has been associated with contact sensitivity; it is also a metabolite of salicin (salicyl alcohol glucoside—see Salix, p. 129.2).

Salverine Hydrochloride *(rINNM)*

Hidrocloruro de salverina; M-811 (salverine); Salverina, hidrocloruro de; Salvérine, Chlorhydrate de; Salverini Hydrochloridum; Сальверина Гидрохлорид.

2-[2-(Diethylamino)ethoxy]-benzanilide hydrochloride.

$C_{19}H_{24}N_2O_3$,HCl=348.9

CAS — 6376-26-7 (salverine).

Profile

Salverine hydrochloride has been used as an antispasmodic in combination preparations for the treatment of biliary-tract disorders, respiratory-tract disorders, and pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Cynarix comp; Montamed; Novipec†.

Salvia Divinorum

Diviner's Sage; Divining Sage; Hierba de María; *Salvia divinorum*; ska María Pastora.

CAS — 83729-01-5 (salvinorin A).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of Salvia divinorum:

Big Sal; heirba Maria; hojas de la Pastora; hojas de Maria; la Maria; La Pastora; LSD Lite; Magic mint; Maria Pastora; Sally D; Salvia; Ska; ska Maria; ska Pastora; The Shepherdess.

Profile

Salvia divinorum has been traditionally used in Mexican Indian culture to induce hallucinations and is now a substance of abuse. Salvinorin A (divinorin A) is the main active constituent.

References.

1. Prisinzano TE. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*. *Life Sci* 2005; **78**: 527–31.
2. Singh S. Adolescent salvia substance abuse. *Addiction* 2007; **102**: 823–4.
3. Paulzen M, Gründer G. Toxic psychosis after intake of the hallucinogen salvinorin A. *J Clin Psychiatry* 2008; **69**: 1501–2.

Sambucus

Bodzavirág; Elder Flower; Fläderblomma; Holunderblüten; Juoduogių šelvamedžių žiedai; Květ bezu černého; Kwiat bzu czarnego; Mustaseljankukka; Sabugueiro; Sambuc; Sambuci flos; Sambuci Nigrae Flos; Saúco; Sureau, fleur de; Бузина.

ATC Herb — HA06AX5009 (Sambucus nigra: fruit); HR05YA5021 (Sambucus nigra: flower); HG04BW5031 (Sambucus nigra: flower).

UNII — 07V4DX094T (Sambucus nigra flower); CT03BSA18U (Sambucus nigra flowering top).

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

Ph. Eur. 8: (Elder Flower). The dried flowers of *Sambucus nigra*. It contains not less than 0.8% of flavonoids, calculated as isoquercitroside with reference to the dried drug. Protect from light.

Profile

Sambucus, in the form of flowers of the elder, *Sambucus nigra* (Black Elder; European Elderberry; European Black Elderberry), has astringent, diaphoretic, and anticatarrhal properties and is used in herbal preparations for a variety of disorders, particularly respiratory-tract disorders. Elder-flower water has been used as a vehicle for eye and skin lotions. Elder-flower ointment has been used as a basis for pomades and cosmetic ointments.

Homoeopathy

Sambucus has been used in homoeopathic medicines under the following names: Sambucus nigra; Sambucus nig; Samb. nig.

General references.

1. WHO. Plos Sambuci. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/26.html (accessed 05/02/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Caj z Kvetu Bezu Cerneho; *Rus.*: Novo-Passit (Ново-Пассит).

Multi-ingredient Preparations. *Arg.*: Gripofit; Yuyo; *Austral.*: DiaCo; HRF; Immune Boost with Andrographis; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; Olive Leaf Plus; Sinupret; *Austria*: Entschlackender Abfuhrtee EF-EM-ES; Grippetee St Severin; Laxalpin†; Sinupret; Solvopret†; Tuscalman; *Canad.*: Honey Herb Cough Drops†; Natraway Sport 1 & 2†; Natraway Sport 3†; Original Herb Cough Drops†; Swiss Herb Cough Drops; *Cz.*: Biotussil; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Novo-Passit; Pulmoran; Reduktan; Sinupret; Species Urologicae Planta; Urcyston Planta; *Fr.*: Hydrastart; Pharyndol; Pharyndol; Santane R_4†; *Ger.*: Sinupret; *Hong Kong*: Sinupret; *Hung.*: Sinupret; Tamarinlax; *Indon.*: Dibost; Elanos Kids; Elanos; Formuno; Glimunos; Idesar Plus; Imboost Force; Imforce Plus; Imforce; Imox; Imufor; Imunogard; Imunvit Plus; Sinupret†; StarMuno; *Ital.*: Atlantis; ETDR; Rinotrofina C; *Malaysia*: Sinupret; *Mex.*: Bisolsinus; Bronkitose Mielimon; *Philipp.*: Sinupret; *Pol.*: Betasol; Infektoten†; Normosan†; Pyrosal; Sinupret; Termasil; *Rus.*: Sinupret (Синупрет); *Singapore*: Sinupret; *Swed.*: Sinova; *Switz.*: Sinupret; Tisane contre les refroidissements; *Thai.*: Sinupret†; *Turk.*: Immuzinc; *UK*: Cleansing Herbs; EP6-C Essence; Hay Fever & Sinus Relief; Hayfever & Sinus Relief; Herb and Honey Cough Elixir; Life Drops; Lion Cleansing Herbs; Lustys Herbalene; Modern Herbals Cold & Catarrh; Sinotar; Sinueeze; Sinuherb; Tabritis; *Ukr.*: Novo-Passit (Ново-Пассит); Sinupret (Синупрет); Urochol (Урохол)†; *Venez.*: Dromil Sauco.

Homoeopathic Preparations. *Austria*: Otovowen; *Canad.*: Aches & Pains; Breathe More; Eczema L87; Homeodel 15†; Sinall Formula†; Snore No More; *Chile*: Similibus; *Fr.*: Allium Cepa Compose; Arnica Complexe no 1; Santaherba; Scabiosa Complexe No 87; Spirodrine; *Ger.*: Lowe-Komplex Nr 13; Otovowen; *Neth.*: Nectadyn H; *Rus.*: Atma (Атма); Sambucus-Plus (Самбукус-Плюс); *S.Afr.*: Sambucus Comp†; *Switz.*: Alceprin-N; Spagyrhin; *Ukr.*: Atma (Атма).

Sandalwood

East Indian Sandalwood; White Sandalwood; Сантал Белый (*Santalum album*).
ATC Herb — HJ01WB5013 (Santalum album: *wood*).
UNII — 3641YW25N2.

Pharmacopoeias. In *Chin.*

Profile

The wood of white sandalwood, *Santalum album* (Santalaceae), has antibacterial and antispasmodic activity and is used in herbal medicine as an adjunct in the treatment of infections of the lower urinary tract. Sandalwood and its preparations contain essential oil.

Sandalwood oil is used in aromatherapy and in perfumery.

References.

1. Burdock GA, Carabin IG. Safety assessment of sandalwood oil (Santalum album L.). *Food Chem Toxicol* 2008; 46: 421–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Brady's-Magentropfen; *Switz.*: Kernosan Eau Dentifrice†; *Ukr.*: Eve Care (Ив Кер)†; Imunin (Имунин)†.

Homoeopathic Preparations. *Fr.*: Santalum Complexe No 30†.

Sanguinaria

Bloodroot; Red Puccoon; Sanguinaria canadensis; Sanguinaris canadensis; Tetterwort; Волчья Стопа Канадская (*Sanguinaria canadensis*).
UNII — B3XJA0OV6T (Sanguinaria canadensis); *N9288CD508* (Sanguinaria canadensis *root*).

NOTE. The name Tetterwort has also been used for Greater Celandine (p. 2522.2).

Profile

Sanguinaria consists of the dried rhizome of *Sanguinaria canadensis* (Papaveraceae). Sanguinarine, an alkaloid extracted from sanguinaria, has been used as an antiplaque agent in toothpaste and mouthwash preparations. Sanguinaria was formerly used as an expectorant but fell into disuse because of its toxicity. Sanguinaria has also been classified by the FDA as a herb that is unsafe for use in foods, beverages, or drugs.

Homoeopathy

Sanguinaria has been used in homoeopathic medicines under the following names: Sanguinaria canadensis; Sang. ca.

Sanguinarium nitrate has been used in homoeopathic medicines under the following names: Sanguinarinum Nitricum; Sang. nit.

Reviews.

1. Karlowsky JA. Bloodroot: Sanguinaria canadensis L. *Can Pharm J* 1991; 124: 260, 262–3, 267.
2. Grenby TH. The use of sanguinarine in mouthwashes and toothpaste compared with some other antimicrobial agents. *Br Dent J* 1995; 178: 254–8.
3. Tenenbaum H, *et al.* Effectiveness of a sanguinarine regimen after scaling and root planing. *J Periodontol* 1999; 70: 307–11.
4. Mackraj I, *et al.* Sanguinarine. *Cardiovasc Ther* 2008; 26: 75–83.
5. Vlachojannis C, *et al.* Rise and fall of oral health products with Canadian bloodroot extract. *Phytother Res* 2012. Available at: doi:10.1002/ptr.4606

Malignant neoplasms of the skin. Self-treatment of basal cell carcinoma on the nasal tip by a 51-year-old man using a topical caustic preparation containing *Sanguinaria canadensis* has been reported.[1] Although a similar caustic paste was originally used in the 1930s as part of Mohs' micrographic surgery (MMS) for some types of skin cancer, the MMS technique in use today is more refined, and self-administration of caustic pastes containing sanguinaria for skin lesions is not recommended. However, such use has continued to be reported and has caused serious skin damage in some patients.[2,3] The Therapeutic Goods Administration[4] in Australia has advised against the use of these preparations which are also marketed as black or red salves.

1. Affleck AG, Varma S. A case of do-it-yourself Mohs' surgery using bloodroot obtained from the internet. *Br J Dermatol* 2007; 157: 1078–9.
2. Saltzberg F, *et al.* Deforming self-treatment with herbal "black salve". *Dermatol Surg* 2009; 35: 1152–4.
3. Glenki JJ, Zaret L. An internet misadventure: bloodroot salve toxicity. *J Altern Complement Med* 2010; 16: 1125–7.
4. Australian Government Department of Health and Ageing: Therapeutic Goods Administration. Black and red salves in treating cancer (issued 19th March, 2012). Available at: http://www.tga.gov.au/safety/alerts-medicine-black-salve-120203.htm (accessed 17/04/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Bronchial Cough; Mielocol†; *Ital.*: Emoform Alifresh; *S.Afr.*: Zeel; Zeel; *Switz.*: Kernosan Eau Dentifrice†.

Homoeopathic Preparations. *Austral.*: Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Respatona Dry Cough & Nasal Congestion; *Austria*: Klimaktoplant; Lymphdiaral; Otovowen; Remens; *Canad.*: Bronchial Cough; Echinacea Compositum; Formula DM 210†; Hea Complex†; Headache & Migraine L77; Homeo-Form ME†; Hylaquell BC; Menopause; Sinusalia; Zeel Comp; *Cz.*: Zeel Compositum; Zeel Salbe†; *Fr.*: Actheane; Phapax; Pulmo-Drainol†; Sepia Compose; *Ger.*: Biodolor; Cefakliman N†; Cefakliman S; Cephaloplant†; Cranio-cyl Ho-Len-Complex; Delto-cyl Ho-Len-Complex; Dolfin; Drosera-Weliplex†; Dularell N; Elana†; Gripps; Klimaktoplant N; Klimax-Gastreu S R10; Lymphdiaral; Meno-cyl L Ho-Len-Complex; Migrane-Gastreu R16; Otovowen; Pflugerplex Gelsemium; Pflugerplex Lemna; Rephalgin N; Zeel comp; *Hung.*: Klimakt-Heel; Zeel; *Neth.*: Cephalite; Homeocare Allerlo; Homeocare neusspray; Homeocare siroop; Klimaktolan; Klimax-Gastreu R10; Lymphdiaral; Zeel comp N; *Rus.*: Klimaktoplan (Климактоплан); Remens (Ременс); Zeel T (Цель Т); *Switz.*: Menosan†; Multiplex I; Regenaplex Nr. 21e; *Ukr.*: Capadol (Кападол); Klimaktoplan N (Климактоплан Н); Remens (Ременс).

Saponins

Sapogenin Glycosides; Saponinai; Saponinas; Saponine; Saponinen; Saponiner; Saponines; Saponiny; Saponosidi; Сапонины.
CAS — 8047-15-2.

Profile

Saponins are a diverse group of plant glycosides that share the property of foaming strongly when shaken with water. They are amphiphilic molecules, consisting of a lipophilic polycyclic aglycone with a hydrophilic sugar side-chain. The aglycone is referred to as a sapogenin and may have either a triterpenoid or steroid structure.

Saponins are found in many plants but common sources include quillaia (p. 2207.1), soapwort (p. 2617.2), yucca (p. 2649.3) and gypsophila (*Gypsophila paniculata* and related species). They are used for their surfactant properties as emulsifying agents (see p. 2164.1) in foods and pharmaceuticals, and have also been used medicinally in preparations for respiratory-tract and other disorders. Saponins and sapogenins with specific pharmacological actions include digoxin (p. 1353.3) and ruscogenin (p. 2608.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Cz.*: Pleumolysin; Tussilen†; *Neth.*: Bronchicum.

Sapropterin Hydrochloride *(rINNM)*

Dapropterin Hydrochloride; Hidrocloruro de sapropterina; Sapropterin Dihydrochloride (USAN); Sapropterin Dihydrochloride (BANM); Sapropterina, hidrocloruro de; Sapropterine, Chlorhydrate de; Sapropterini Hydrochloridum; SUN-0588 (sapropterin or sapropterin hydrochloride); T-1401; (6*R*)-5,6,7,8-Tetrahydrobiopterin Hydrochloride; Сапроптерина Гидрохлорид.
(-)-(6*R*)-2-Amino-6-[(1*R*,2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(3*H*)-pteridinone dihydrochloride.
$C_9H_{15}N_5O_3.2HCl$=314.2
CAS — 62989-33-7 (sapropterin); 69056-38-8 (sapropterin hydrochloride).
ATC — A16AX07.
ATC Vet — QA16AX07.
UNII — RG277LF583.

Profile

Sapropterin is the synthetic form of tetrahydrobiopterin (BH_4), an endogenous cofactor for phenylalanine hydroxylase. It is used for the treatment of hyperphenylalaninaemia due to phenylketonuria (p. 2042.2) or tetrahydrobiopterin deficiency.

Sapropterin is given orally as the hydrochloride in a single daily dose with food, preferably in the morning. The initial daily dose in patients 4 years of age and above with *phenylketonuria* is 10 mg/kg adjusted until adequate phenylalanine concentrations have been achieved; usual maintenance daily doses are 5 to 20 mg/kg. The initial daily dose in patients 4 years of age and above with *tetrahydrobiopterin deficiency* is 2 to 5 mg/kg, adjusted up to 20 mg/kg daily as required; it may be necessary to distribute the dose over the day as 2 or 3 divided doses.

References.

1. Opladen T, *et al.* Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria. *Eur J Pediatr* 2005; 164: 395–6.
2. Feillet F, *et al.* Pharmacokinetics of sapropterin in patients with phenylketonuria. *Clin Pharmacokinet* 2008; 47: 817–25.
3. Sanford M, Keating GM. Sapropterin: a review of its use in the treatment of primary hyperphenylalaninaemia. *Drugs* 2009; 69: 461–76.
4. Trefz FK, *et al.* Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study. *J Pediatr* 2009; 154: 700–7.
5. Hegge KA, *et al.* Sapropterin: a new therapeutic agent for phenylketonuria. *Ann Pharmacother* 2009; 43: 1466–73.
6. Somaraju UR, Merrin M. Sapropterin dihydrochloride for phenylketonuria. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 06/08/10).

Administration in children. For doses in children 4 years of age and over, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Kuvan; *Austria*: Kuvan; *Belg.*: Kuvan; *Canad.*: Kuvan; *China*: Kuvan (科望); *Cz.*: Kuvan; *Denm.*: Kuvan; *Fr.*: Kuvan; *Ger.*: Kuvan; *Gr.*: Kuvan; *Hung.*: Kuvan; *Irl.*: Kuvan; *Israel*: Kuvan; *Jpn*: Biopten; *Neth.*: Kuvan; *Norw.*: Kuvan; *NZ*: Kuvan; *Pol.*: Kuvan; *Port.*: Kuvan; *Spain*: Kuvan; *Swed.*: Kuvan; *Switz.*: Kuvan; *UK*: Kuvan; *USA*: Kuvan.

Sarsaparilla

Raíz de zarzaparrilla; Salsaparilha; Salsepareille; Sarsa; Sarsaparilla Root; Smilacis Rhizoma; Zarzaparrilla; Сассапариль.
UNII — H51N91QNE8 (Smilax glabra); *PE53YXA3LR* (Smilax glabra *tuber*).

Pharmacopoeias. In *Chin.* and *Jpn.*, which specify *Smilax glabra*.

Profile

Sarsaparilla is the dried root of various species of *Smilax* (Liliaceae). It has been used, usually in the form of a decoction or extract, as a vehicle and flavour for medicaments. It is also an ingredient of herbal preparations

Homoeopathy

Sarsaparilla has been used in homoeopathic medicines under the following names: Smilax; Sarsap.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Urinefrol; *Austral.*: Derma-Co; *Braz.*: Galenogal; *Canad.*: Depuratif des Trappistes; Eliminex; Herbanat†; *Indon.*: Instink†; Provigor†; *Ital.*: Tisana Kelemata; *UK*: Gerard House Reumalex; HRI Clear Complexion; Jamaican Sarsaparilla; Napiers Oral Skin Soother Herbal Relief; Skin Eruptions Mixture; *USA*: Detox.

Homoeopathic Preparations. *Austria*: Erbiode Blasen und Nieren; *Canad.*: Common Mallow Combination†; Yellow Dock Combination†; *Cz.*: Lymphomyosot; *Fr.*: Calendula Complexe No 89; Formica Rufa Compose; Pareira Brava Compose; Saponaria Compose; *Ger.*: Derivatio H; Derivatio; Haut-Gastreu R60; Jsostoma S; Lymphomyosot N; Lymphomyosot; Pascorenal N; uro-loges; Uroselect; Urotruw N; *Hung.*: Pro-Aller; *Neth.*: Restructa H; *S.Afr.*: Lymphomyosot; *Ukr.*: Lymphomyosot (Лімфомиозот); Lymphomyosot N (Лімфомиозот Н).

Sassafras Oil

Oleum Sassafras; Sasafrás, aceite esencial de; Сассафрасовое Масло.
ATC Herb — HA03AW5053 (Sassafras albidum: *essential oil*); *HM02AW5019* (Sassafras albidum: *essential oil*); *HP03AX5004* (Sassafras albidum: *essential oil*).
UNII — 78ZX2PFG2Z.

Uses and Administration

Sassafras oil is a volatile oil distilled from the root or root bark of *Sassafras albidum* (Lauraceae), or from the wood of certain species of *Ocotea* (Lauraceae). It contains safrole.

Sassafras oil has rubefacient properties and was formerly used as a pediculicide.

Adverse Effects

Neither sassafras nor the oil should be taken internally; the use of herb teas of sassafras may lead to a large dose of safrole. The use of safrole in foods has been banned because of carcinogenic and hepatotoxic risks. The use of safrole in toilet preparations is also controlled.

Poisoning. A 47-year-old woman experienced 'shakiness', vomiting, anxiety, tachycardia, and raised blood pressure after ingestion of a potentially fatal dose of sassafras oil (5 mL). She was given activated charcoal and symptomatic management.[1]

1. Grande GA, Dannewitz SR. Symptomatic sassafras oil ingestion. *Vet Hum Toxicol* 1987; 29: 447.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Inhalador Medex; *Cz.*: Stopangin; Stopangin; *Hong Kong*: Sloan's Liniment†; *Indon.*: Thymcal; *Rus.*: Stopangin (Стопангин); *S.Afr.*: Moultons Pain Paint†; Zam-Buk; *Ukr.*: Stopangin (Стопангин); Stopangin (Стопангин).

Satavaptan *(rINN)* ⊗

Satavaptan; Satavaptanum; SR-121463 (satavaptan); SR-1214638 (satavaptan phosphate); Сатавптан.

N-tert-Butyl-4-{[(cis-5′-ethoxy-4-[2-(morpholin-4-yl)ethoxy]-2′-oxo-1′,2′-dihydrospiro[cyclohexane-1:3′-indole]-1′-yl)sulfonyl]-3-methoxybenzamide.

$C_{33}H_{45}N_3O_8S$=643.8

CAS — 185913-78-4 (satavaptan); 308145-17-7 (satavaptan phosphate).

UNII — AJS853P31H.

Profile

Satavaptan is a selective vasopressin V_2-receptor antagonist that has been investigated for the treatment of hyponatraemia in the syndrome of inappropriate antidiuretic hormone sécretion.

References.

1. Soupart A, *et al.* Successful long-term treatment of hyponatremia in *syndrome of inappropriate antidiuretic hormone secretion with* satavaptan (SR121463B), an orally active nonpeptide vasopressin V_2-receptor antagonist. *Clin J Am Soc Nephrol* 2006; 1: 1154–60.

Saxitoxin

Saxitoxina.

CAS — 35523-89-8.

Profile

Saxitoxin is a neurotoxin associated with paralytic shellfish poisoning. It is an endotoxin produced by species of dinoflagellate plankton present in infected molluscs.

References.

1. Halstead BW, Schantz EJ. *Paralytic shellfish poisoning.* Geneva: WHO, 1984.
2. WHO. Aquatic (marine and freshwater) biotoxins. *Environmental Health Criteria* 37. Geneva: WHO,1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc37.htm (accessed 24/07/08)
3. Hartigan-Go K, Bateman DN. Reddide in the Philippines. *Hum Exp Toxicol* 1994; 13: 824–30.
4. Gessner BD, *et al.* Hypertension and identification of toxin in human urine and serum following a cluster of mussel-associated paralytic shellfish poisoning outbreaks. *Toxicon* 1997; 35: 711–22.
5. de Carvalho M, *et al.* Paralytic shellfish poisoning: clinical and electrophysiological observations. *J Neurol* 1998; 245: 551–4.
6. Lehane L. Paralytic shellfish poisoning: a potential public health problem. *Med J Aust* 2001; 175: 29–31.
7. Garcia C, *et al.* Paralytic shellfish poisoning: post-mortem analysis of tissue and body fluid samples from human victims in the Patagonia fjords. *Toxicon* 2004; 43: 149–58.
8. Llewellyn LE. Saxitoxin, a toxic marine natural product that targets a multitude of receptors. *Nat Prod Rep* 2006; 23: 200–22.

Schick Test

Prueba de Schick; Реакция Шика.

Pharmacopoeias. *Br.* include standards for Schick test toxin and control.

BP 2014: (Schick Test Toxin). It is prepared from a toxigenic strain of *Corynebacterium diphtheriae*. It contains a suitable antimicrobial preservative. Store at 2 degrees to 8 degrees.

BP 2014: (Schick Control). It is Schick Test Toxin that has been heated at a temperature not lower than 70 degrees and not higher than 85 degrees for not less than 5 minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is to be used. Store at 2 degrees to 8 degrees.

Profile

Intradermal injection of Schick test toxin has been used for the diagnosis of susceptibility to diphtheria and, more importantly, to detect patients who might have an adverse reaction to diphtheria vaccines. Children up to the age of about 8 to 10 years rarely suffer from such reactions and therefore the Schick test is not usually performed in this age group. In older children and adults a Schick test was formerly used before the use of standard diphtheria vaccines. However, diphtheria vaccines for use in adults and adolescents (p. 2382.3) are now formulated with lesser amounts of toxoid so Schick testing is unnecessary.

Schisandra

Schizandra; Лимонник; Шизандра.

Pharmacopoeias. *Chin.* includes the dried ripe fruit of *Schisandra chinensis* (Fructus Schisandrae Chinensis) and *S. sphenanthera* (Fructus Schisandra Sphenanthera)

Eur. (see p. vii) and *Jpn* include the fruit of *S. chinensis*.

Ph. Eur. 8: (Schisandra Fruit). The whole, dried, or steamed and dried, ripe fruit of *Schisandra chinensis*. It contains a minimum of 0.40% schisandrin ($C_{24}H_{32}O_7$=432.5) calculated with reference to the dried drug. Protect from light.

Profile

The dried ripe fruit of *Schisandra chinensis* or *S. sphenanthera*, sometimes referred to as schizandrae fructus, are known in Chinese medicine as wuweizi and nanwuweizi respectively. Schisandra is used in a variety of disorders and contains lignans claimed to have protective effects on the liver. The oil is also used.

The derivative bifendate has been reported to interact with ciclosporin (see p. 1953.2). SchE (*Hezheng Pharmaceutical Company, China*), an extract of *Schisandra sphenanthera* containing amongst other ingredients deoxyschizandrin, is reported to be an inhibitor of cytochrome P450 isoenzymes of the CYP3A subfamily, and has been reported to increase maximum blood concentrations of tacrolimus (see p. 1973.3).

References.

1. Panossian A, Wikman G. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. *J Ethnopharmacol* 2008; 118: 183–212.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Bacopa Complex; Echinacea Royale; Herbal Rest & Relax; LivCo; Liver Detox; Liver Tonic Complex; Mindac; Nevaton; PM Syrin; *Indon.*: Bio-Curliv; Curliv Plus; Curliv Plus; Curliv; Hepa-Q; Hepacell†; Hepamax; Naturliver; Sanoliv; *Jpn*: Ryokankyomishingeninto; Seihaito; Seishoekkito; *Pol.*: Penigra; *Rus.*: Carmolis (Кармолис); Theravit Tonic (Теравит Тоник); *Swed.*: Chisan; Chisandra; *Ukr.*: PM Sirin (ПМ Сирин); Theravit Tonic (Теравит Тоник)†; *USA*: Adrenoid.

Schoenocaulon Officinale

Caustic Barley; Cevadilla; Cévadille; Sabadilla; Sabadillgermer.

UNII — QLC7BUA4V8 (Schoenocaulon officinale); 6NAF1689IO (Schoenocaulon officinale seed).

Profile

The dried seeds of *Schoenocaulon officinale* (*Veratrum officinale*) (Melanthiaceae) contain a number of alkaloids and are a source of veratrine (see p. 2644.2). They were formerly used as a topical insecticide. Preparations of the seeds have also been given internally as an anthelmintic and for rheumatism, but were generally considered to be too toxic for medicinal use either topically or systemically. Overdose has been fatal. Schoenocaulon has also been used in veterinary medicine and as an environmental insecticide.

Homoeopathy

Schoenocaulon officinale has been used in homoeopathy.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Hay Fever; *Austria*: Apozema Apis compositum; Erbiode Heuschnupfen; Famulan; Ferrum Phosphoricum comp; Infludo; *Canad.*: Adrisin†; Allergies; Allergy Relief†; Comp-Drops 5 Expectorant†; Coryzalia; Formula INF; Hay Complex†; Hay Fever; Hayfever; Homeo-Form AL†; Homeodel 15†; Hylamine HF; Kids Allergies; Sabalia; Sinus Ease; Sinuspax†; *Chile*: Allium Compuesto; Rinoplex; *Cz.*: Coryzalia; Rhinallergy; *Fr.*: Coryzalia; Dolistamine†; Infludo; Phytogargarisme†; Rhinallergy; Sinuspax; *Ger.*: Allergokatt; Ferrum phosphoricum comp; Gripps; Infludo; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Psychoneuroticum (Rowo-578)†; Sinapis nigra N Oligoplex; Vertizin; *Hung.*: Coryzalia; PSY-Stabil; *Neth.*: Coryzalia; Grippe-Gastreu R6; Infludo; PSY-stabil; *Port.*: Coryzalia; *Rus.*: Coryzalia (Корризалия); Famulan (Фамулан); *S.Afr.*: Ferrum Phos Comp†; Infludo†; *Switz.*: Coryzalia; Gouttes contre les rhumes des foins†; Infludo; Nelsons Pollenna†; Rhinallergy; Sinuspax†; *UK*: Infludo; Pollenna; *Ukr.*: Coryzalia (Корризалия); *USA*: Preferred Remedies Allergy.

Scoparium

Broom Tops; Genêt; Genêt à Balai; Planta Genista; Retama negra; Scoparii Cacumina; Жарновец Метельчатый (*Sarothamnus scoparius*).

ATC Herb — HC01EB5014 (Cytisus scoparius: herb); HG04BW5008 (Cytisus scoparius: herb).

UNII — XZC6HBR666 (Cytisus scoparius flowering top).

Pharmacopoeias. In *Fr.*

Profile

Scoparium is the dried tops of broom, *Sarothamnus scoparius* (*Cytisus scoparius*) (Leguminosae). It is a mild diuretic, haemostatic, and vasoconstrictor and has been given as a decoction or alcoholic extract. It has oxytocic properties and should be avoided in pregnancy. It contains sparteine (p. 2621.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Spartiol†.

Multi-ingredient Preparations. *Fr.*: Rap Phyto; *Pol.*: Fitoven.

Homoeopathic Preparations. *Austria*: Aurumheel; Rytmopasc; *Canad.*: Tyglan†; *Ger.*: Arrhythmie-Gastreu N; Derivatio H; Derivatio; Hypotonie-Gastreu R44; Rytmopasc; Spartiol Cardio; *Hung.*: Aurumheel; *Neth.*: Cralonin H.

Scopolia

Belladonna Scopola; Dårört; European Scopolia; Glockenbilsenkraut; Krainer Tollkraut; Russian Belladonna; Scopola; Scopolia Rhizome; Scopoliae Rhizoma; Tollkraut.

UNII — D5E3O48XGC (Scopolia carniolica root); 04AC8ASX63 (Scopolia japonica); R2649T2OOV (Scopolia parviflora).

NOTE. Distinguish from Belladonna, p. 2453.3. The name Japanese belladonna has been applied to *Scopolia carniolica* but is more correctly applied to *S. japonica*.

Pharmacopoeias. In *Jpn.*, which defines scopolia as the rhizome and root of *Scopolia japonica, Scopolia carniolica*, or *Scopolia parviflora*.

Profile

The root of *Scopolia carniolica* (Solanaceae) contains alkaloids with antimuscarinic activity, mainly hyoscyamine, and has actions similar to those of belladonna (see p. 2453.3). Alkaloids are also present in the leaves.

It is included in herbal preparations for gastrointestinal, biliary, and urinary-tract spasm.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Magesto; *Jpn*: Cabagin S New; *Thai.*: Diasgest; Digestin; Magesto; Mesto-Of.

Sea Buckthorn

Argousier; Sallowthorn; Sea-buckthorn; Облепиха Крушиновидная.

NOTE. Distinguish from Alder Buckthorn Bark (see Frangula Bark, p. 1843.3) and from Buckthorn (p. 1824.2).

Profile

Sea buckthorn (*Hippophae rhamnoides*, Eleagnaceae) is used in traditional medicine and is the source of sea buckthorn oil, p. 2612.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Hiporhamin (Гипорамин); *Ukr.*: Erebra (Эребра).

Multi-ingredient Preparations. *Rus.*: Hyporolam (Гипоролам); Sodecor (Содекор).

Sea Buckthorn Oil

Облепиховое Масло.

Profile

Sea buckthorn oil is extracted from the seeds and berries of sea buckthorn (p. 2611.3) and has been taken orally for skin and mucous membrane disorders and as a tonic. It has also been investigated in liver fibrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Omega 7.

Multi-ingredient Preparations. *Fr.*: Alphalarm; Hydromega; *Rus.*: Olasol (Олазоль); Olestesin (Олестезин).

Sea Water

Aqua marina.

Sea Salt

UNII — 87GE52P74G.

Profile

Sea water is water obtained from a sea or ocean. It contains sodium chloride (p. 1795.1) and other essential minerals and trace elements; the sodium chloride content is about 3.5%, although this varies depending on the source. Processed sea water has been used as a dietary mineral supplement and as a solution for nasal irrigation, either undiluted or as an isotonic solution.

Sea salt is obtained by evaporation of sea water and contains sodium chloride and other minerals. It has been used similarly to sea water in preparations for nasal disorders. It also has widespread culinary uses.

Homoeopathy

Sea water has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Demazin Saline; Otrivin Sea Water; Sinoclear; *Belg.*: Lyomer Plus; *Canad.*: Hydrasense; Rhinaris Sinomarin; *Chile*: Fisiomar; Sinomarin; Sterimar†; *Fr.*: Audi Baby; Audiclean; Audispray; Docuspray; Fanomer; Marimer†; Physiomer; Plasma du Dr Quinton†; Proceane Hypertonique†; Quies auriculaire†; Selgine; Sinomarin†; Sterimar; Thalamag; *Ger.*: Rhinomer†; Rhinospray Atlantik†; Rinupret; *Gr.*: Physiomer; *Hong Kong*: Sinomarin; Sterimar; *Hung.*: Solimar; Sterimar; *Irl.*: Sterimar†; *Israel*: Drossanose†; Rhinomer; Sterimar; *Ital.*: Physiomer; Sterimar; *Malaysia*: Sterimar; *Mex.*: Allemar Nasalmer; Sterimar; *Philipp.*: Physiomer; *Rus.*: Aqua Maris (Аква Марис); Fluimarin (Флуимарин); Marimer (Маример); Morenazal (Моренazal); Physiomer (Физиомер); *Singapore*: Sinomarin; Sterimar; *Switz.*: Drossa-Nose; Fluimare; Nose Fresh; Otrivin Mer; Rhinomer; Siccoral; Sinomarin; Triomer; *Turk.*: Lyomer†; Rhinomer; Sinomarin; Sterimar; Tonimer; *UK*: Sterimar; *Ukr.*: Aqua Maris (Аква Марис); Humer (Хьюмер); Marimer (Маример); Quixx (Квикс).

Multi-ingredient Preparations. *Austral.*: Otrivin Saline Plus; *Fr.*: Marinol; Thalamag fer B_9; *Ger.*: Aliamare; Siozwo San; Weleda-Rheumasalbe M†; *Hong Kong*: Mar Plus; *Hung.*: Yam; *Ital.*: Kamillosan Ocean; Respifree; Sterimar Cu; Sterimar Mn; *Malaysia*: Mar Plus; *Rus.*: Doppelherz Energotonik (Доппельгерц Энерготоник); *Switz.*: Fluimare Plus; Narifresh; Nasmer 3plus; Nasmer free; Nose Fresh au D-panthenol; Nose Fresh; Rhinomer mini; Siccalix; *Thai.*: Mar Plus; Marimer; *UK*: Allerclear.

Seaweeds, Kelps, and Wracks

UNII — 477TV3P5UX (seaweed).

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

Ph. Eur. 8: (Kelp; Fucus vel Ascophyllum). The fragmented dried thallus of *Fucus vesiculosus* or *F. serratus* or *Ascophyllum nodosum*. It contains not less than 0.03% and not more than 0.2% of total iodine, calculated with reference to the dried drug. It has a salty and mucilaginous taste, and an unpleasant marine odour. Protect from light.

The Ph. Eur. title was formerly Bladderwrack and the BP 2014 gives Bladderwrack and Fucus as approved synonyms.

Uses and Administration

Dried seaweeds of various species are used in herbal preparations.

The terms kelps and wracks have been used indiscriminately for each other and other brown seaweeds. For example, Kelp (Ph. Eur. 8) refers to a preparation of various species of wrack and was formerly titled Bladderwrack.

Bladder wrack (*Fucus vesiculosus*), toothed wrack (*F. serratus*), or knotted wrack (*Ascophyllum nodosum*) are included in preparations given for various disorders including obesity, constipation, and iodine deficiency.

Kelps refer properly to species of *Laminaria* and *Macrocystis*. They are present as an ingredient of several dietary supplements and herbal preparations, including for use in obesity; they have also been used as a source of iodine. Laminaria stalks (p. 2540.1) are used for dilation of cavities or the cervix.

Fucoidan (p. 2508.1) is a sulfated polysaccharide extracted from brown seaweeds. Carrageenan (p. 2176.3) may be extracted from red seaweeds.

Homoeopathy

Fucus vesiculosus has been used in homoeopathic medicines under the following names: Fucus; Fucus v.

Adverse Effects and Precautions

Kelp can concentrate various heavy metals; auto-immune thrombocytopenic purpura and disordered erythropoiesis in a patient who had been taking kelp tablets for 6 weeks was attributed to the arsenic content of the preparation.[1]

Clinical hyperthyroidism has also been reported in patients taking kelp-containing preparations as part of a slimming regimen[2] or a dietary supplement.[3]

The FDA has advised that preparations containing compounds such as kelp, which may be taken orally in bulk laxatives or weight-control preparations, should be taken with a full glass of water or, if the patient has difficulty in swallowing, they should be avoided. Such compounds swell into masses that may obstruct the oesophagus if not taken with sufficient water.

1. Pye KG, *et al.* Severe dyserythropoiesis and autoimmune thrombocytopenia associated with ingestion of kelp supplements. *Lancet* 1992; 339: 1540.
2. de Smet PA, *et al.* Hyperthyreoïdie tijdens het gebruik van kelp tabletten. *Ned Tijdschr Geneeskd* 1990; 134: 1058–9.
3. Eliason BC. Transient hyperthyroidism in a patient taking dietary supplements containing kelp. *J Am Board Fam Pract* 1998; 11: 478–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sual; *Braz.*: Redufat†; *Canad.*: Thyodyn; *Fr.*: Algues†; Dictyolone; *UK*: Adios Max.

Multi-ingredient Preparations. *Arg.*: Adelgacin; Arceligasol; Cellasene Gold; Cellasene†; Celu-Atlas; Centella Queen Complex; Centellase de Centella Queen; Centellase Gel; Dermasolutions†; Desgras Complex; Desgras; Herbaccion Celfin; Herbaccion Diet; KLB6 Fruit Diet; Natural Diet; Nio Marine; Redualgas; Silueta Plus†; Varisedan Gel; Yerba Diet; *Austral.*: Daily Plus Max†; PMT-Eze†; Zellulean with Escin†; *Canad.*: Floradix Tab†; Kyolic 101†; Saw Palmetto Formula†; Trim-Fit†; *Chile*: Cellenergy; Celltech; Celu-Atlas; *Cz.*: Reduktan; *Fr.*: Boribel Tisane No 9; Cyclotelia; Dellova†; Dragees Fuca; Duo Reparation; Elusanes Algues brunes/aloes†; Marinol; Mediflor no 1; Menoliistica; Neurovitol; Obeflorine†; Provencale No 2†; Tisane Provencale no 2†; *Hong Kong*: Slimming Aid†; *Hung.*: Metabol; *Indon.*: DFM; *Ital.*: Altadrine Firming†; Fave di Fuca; Skarflex; *Pol.*: Herbaton†; *S.Afr.*: Activex 40 Plus†; *Singapore*: Scar Esthetique; Vitaton; *Spain*: Lipograsil†; *UK*: Adios; Aquella; Boldex; Gerard House Water Relief Tablets; HealthAid Boldo-Plus; Kelp Plus 3; Pure Plan; Water Naturtabs; Weight Loss Aid; *Ukr.*: Mammoleptin (Маммолептин); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Adrenoid; KLB6; *Venez.*: Demerung; Fugras; Lecivar Plus.

Homoeopathic Preparations. *Austria*: Gracil; *Canad.*: Formula Homeo QR 209†; Fucus L111†; Homeo-Form S†; Lympatox; Weight Control; Weight Loss Kit†; *Chile*: Fucus Especial; *Fr.*: Fucus Complexe No 111; *Ger.*: Adiporell; Fucus-Gastreu S R59; Thyreo-Pasc; *Switz.*: Regenaplex Nr. 71b; *Venez.*: Strumeel T.

Secretin *(BAN, USAN, rINN)*

Secretina; Sécrétine; Secretinum; Sekretiini; Sekretin; Секретин.

CAS — 17034-35-4 (porcine); 108153-74-8 (human).
ATC — V04CK01.
ATC Vet — QV04CK01.
UNII — 88C55N56UU (secretin); A0426J905J (secretin human).

Units

The potency of secretin may be expressed as Crick-Harper-Raper (CHR) units based on the pancreatic secretion in *cats* or as clinical units, the value of which was amended in the 1960s. One clinical unit is considered to be equivalent to about 4 CHR units. One clinical unit is equivalent to 200 nanograms of a purified synthetic preparation of secretin.

Uses and Administration

Secretin is a polypeptide hormone involved in the regulation of gastric function. It may be prepared from the duodenal mucosa of *pigs*; synthetic human and porcine versions are also available. On intravenous injection it causes an increase in the secretion by the pancreas of water and bicarbonate into the duodenum.

Secretin is used as a diagnostic agent in various disorders of the pancreas. Patients should be given an initial intravenous test dose of 1 or 2 clinical units (200 or 400 nanograms); if no hypersensitivity reaction is noted after 1 minute, the diagnostic dose may be given.

Secretin is used alone, or with pancreozymin (p. 2582.) or other cholecystokinetic agents such as ceruletide (p. 2473.3) or sincalide (p. 2616.3), as a test for exocrine pancreatic function (see under Pancreatitis, p. 2580.2). The test usually involves duodenal intubation of the patient and examination of duodenal aspirate. The diagnostic dose of secretin used has varied but common doses have been 1 clinical unit/kg (200 nanograms/kg) given by slow intravenous injection.

Patients with the Zollinger-Ellison syndrome (p. 1814.) show an increase in gastrin when given secretin; this is in contrast to a small change or no effect in subjects without the disorder. The usual dose of secretin for the diagnosis of Zollinger-Ellison syndrome is 2 clinical units/kg (400 nanograms/kg) by slow intravenous injection. Serum-gastrin concentrations are measured for up to 30 minutes following the diagnostic dose.

Secretin is also used in a dose of 1 clinical unit/kg (200 nanograms/kg) by slow intravenous injection as an aid in the identification of the pancreatic ducts in patients undergoing endoscopic retrograde cholangiopancreatography.

Autism. There have been anecdotal reports of improvement in behaviour in autistic children given porcine secretin. However, a double-blind placebo-controlled study[1] involving 60 children with autism or pervasive developmental disorder noted no benefit over 4 weeks after a single infusion of 400 nanograms/kg of synthetic human secretin. A randomised, placebo-controlled study[2] in 61 children with autism has similarly found no evidence of efficacy from 2 repeated doses of porcine secretin. Further controlled studies have likewise failed to show efficacy.[3,4]

1. Sandler AD, *et al.* Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. *N Engl J Med* 1999; 341: 1801–6.
2. Roberts W, *et al.* Repeated doses of porcine secretin in the treatment of autism: a randomized, placebo-controlled trial. Abstract: *Pediatrics* 2001; 107: e71. Full version: http://pediatrics.aappublications.org/cgi/reprint/107/5/e71.pdf (accessed 16/08/10)
3. Levy SE, *et al.* Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin. *Arch Dis Child* 2003; 88: 731–6.
4. Coplan J, *et al.* Children with autistic spectrum disorders. II: parents are unable to distinguish secretin from placebo under double-blind conditions. *Arch Dis Child* 2003; 88: 737–9.

Adverse Effects

Adverse effects reported with secretin include flushing, nausea, vomiting, and abdominal pain. There is the potential for hypersensitivity reactions to occur.

Precautions

The secretin test should be avoided in patients with acute pancreatitis. Patients should receive an intravenous test dose because of the risk of hypersensitivity reactions. Results of the secretin test should be interpreted with caution in patients who have had a vagotomy, who have inflammatory bowel disease, or who are receiving anticholinergics at the time of the test because they may be hyporesponsive to secretin stimulation. Conversely, patients with alcoholic or other hepatic impairment occasionally show a greater than normal response to secretin stimulation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Secrelux; *Gr.*: Secrelux; *USA*: ChiRhoStim.

Senecio

Крестовник Якова (*Senecio jacobaea*); Крестовник Золотистый (*Senecio aureus*).

ATC Herb — HG04BW5036 (Senecio aureus: herb); HG02WA5003 (Senecio aureus: herb).
UNII — 5WS1632J8W (Senecio aureus).

NOTE. The common name tansy ragwort has also been used for *Senecio jacobaea* and should not be confused with tansy, which is *Tanacetum vulgare* (see p. 2625.3).

Profile

The ragwort, *Senecio jacobaea*, and, in the USA, the golden ragwort (golden senecio; liferoot; squaw weed), *S. aureus* (Compositae), have been used in the form of extracts as emmenagogues but are of doubtful value. Ragwort, in the form of a decoction or ointment, has also been applied externally to aid wound healing and in the treatment of peripheral vascular disorders.

Many species of the genus *Senecio*, which includes the ragworts and groundsels, are poisonous. They have been found to contain pyrrolizidine alkaloids, which produce hepatic necrosis. The ragwort, *S. jacobaea*, which is abundant throughout the British Isles, is poisonous to livestock when eaten in quantity. Poisoning has also been reported in humans after ingestion of herbal teas containing pyrrolizidine alkaloids. In the UK, the sale, supply, or importation of unlicensed medicinal products containing *Senecio* spp. for internal use is prohibited.

Homoeopathy

Golden ragwort has been used in homoeopathic medicines under the following names: Senecio aur.; Senecio aureus; Sen. aur..

Ragwort has been used in homoeopathic medicines under the following names: Senecio jacobaea; Senecio jac.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Pascofemin; *Canad.*: Motherwort Combination 1†; *Cz.*: Hormeel S; *Fr.*: L 25; Sclerocalcine; *Ger.*: Pascofemin; *Hung.*: Hormeel S; *USA*: Succus Cineraria Maritima†.

Senicapoc *(USAN, rINN)*

17043; ICA-17043; Sénicapoc; Senicapocum; Сеникапок.
2,2-bis (4-Fluorophenyl)-2-phenylacetamide.
$C_{20}H_{15}F_2NO$=323.3
CAS — 289656-45-7.
UNII — T56G201A6Q.

Profile

Senicapoc is an inhibitor of the Gardos calcium-activated potassium channel that is under investigation as an oral treatment for asthma. It has also been investigated to prevent the dehydration of red cells in sickle-cell anaemia.

References.

1. Ataga KI, *et al.* Efficacy and safety of the Gardos channel blocker, senicapoc (ICA-17043), in patients with sickle cell anemia. *Blood* 2008; 111: 3991–7.
2. Ataga KI, Stocker J. Senicapoc (ICA-17043): a potential therapy for the prevention and treatment of hemolysis-associated complications in sickle cell anemia. *Expert Opin Invest Drugs* 2009; 18: 231–9.

Senlizumab *(BAN)*

Bay-10-3356; Bay-w-3356; CDP-571; Сенлизумаб.
CAS — 336128-48-4.

NOTE. The name Humicade has been used as a trade mark for senlizumab.

Profile

Senlizumab is a humanised monoclonal antibody to tumour necrosis factor. It has been investigated in the treatment of Crohn's disease, ulcerative colitis, and rheumatoid arthritis.

References.

1. Rankin EC, *et al.* The therapeutic effects of an engineered human anti-tumour necrosis factor alpha antibody (CDP571) in rheumatoid arthritis. *Br J Rheumatol* 1995; 34: 334–42.
2. Evans RC, *et al.* Treatment of ulcerative colitis with an engineered human anti-TNF alpha antibody CDP571. *Aliment Pharmacol Ther* 1997; 11: 1031–5.
3. Stack WA, *et al.* Randomised controlled trial of CDP571 antibody to tumour necrosis factor-α in Crohn's disease. *Lancet* 1997; 349: 521–4.
4. Anonymous. CDP 571: anti-TNF monoclonal antibody, BAY 103356, BAY W 3356, Humicade. *Drugs R D* 2003; 4: 174–8.
5. Sandborn WJ, *et al.* CDP571, a humanised monoclonal antibody to tumour necrosis factor α, for moderate to severe Crohn's disease: a randomised, double blind, placebo controlled trial. *Gut* 2004; 53: 1485–93.
6. Mamula P, *et al.* CDP571, a humanized anti-tumor necrosis factor-alpha monoclonal antibody in pediatric Crohn's disease. *Inflamm Bowel Dis* 2004; 10: 723–30.
7. Feagan BG, *et al.* A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, in patients with corticosteroid-dependent Crohn's disease. *Aliment Pharmacol Ther* 2005; 21: 373–84.
8. Feagan BG, *et al.* CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; 23: 617–28.

Sepia

UNII — QDL83WN8C2.

Profile

Sepia is the dried inky secretion of the cuttle fish.

Homoeopathy

Sepia has been used in homoeopathic medicines under the following names: Sepia officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Femi-Nan; Nervatona Calm; Nervatona Focus; *Thai.*: Venium.

Homoeopathic Preparations. *Austral.*: Homoderma; Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; Nervatona Calm; Nervatona Focus; Respatona Nasal Spray Decongestant; Travellers Relief; *Austria*: Haemex; Klimaktoplant; Mefem; Nervoheel; Orgafem; Remens; Sulfur Med Complex; *Canad.*: Eczema; Formula CA 205†; Men Complex†; *Chile*: Lachesis; *Cz.*: Hormeel S; Vita C-R15 forte†; Vita C-R15†; *Fr.*: Abbe Chaupitre no 23†; Abbe Chaupitre no 30†; Abbe Chaupitre no 59†; Helonias Compose; Sepia Complexe No 20; Sepia Compose; *Ger.*: Ambrax; Cefakliman S; Cefakliman†; Dermi-cyl L Ho-Len-Complex; HanoFemin; Infi-China; Infi-Symphytum; Infifer N; Klimaktoplant N; Meno-cyl L Ho-Len-Complex; Sepia comp; *Hung.*: Hormeel S; Klimakt-Heel; Nervoheel; *Neth.*: Homeocare Cyclo; Homeocare Nervo; Hormeel H; Klimaktolan; Mulimen H; Nervofleur; Nervoheel; *Rus.*: Hormeel SN (Гормель CH); Klimaktoplan (Климактоплан); Remens (Ременс); *Switz.*: Menosan†; Nervoheel; *Ukr.*: Homvio-Nervin (Хомвио-Нервин); Klimaktoplan N (Климактоплан H); Remens (Ременс); *USA*: Estrex.

Serotonin

Enteramina; Enteramine; 5-Hidroxitriptamina; 5-HT; 5-Hydroxytryptamine; Serotonina; Серотонин.
3-(2-Aminoethyl)-1*H*-indol-5-ol.
$C_{10}H_{12}N_2O$=176.2
CAS — 50-67-9.
UNII — 333DO1RDJY.

Profile

Serotonin, which is synthesised in the body from the essential amino acid tryptophan, is found in the brain, blood platelets, and throughout the gastrointestinal tract. It acts as a biochemical mediator and its roles include involvement in CNS neurotransmission, haemostasis, vascular spasm, and gastrointestinal motility. Abnormalities within the serotonin system are associated with a variety of disorders and many drugs have been developed to manipulate serotonin concentrations.

Serotonin itself may be of value in the treatment of posthypoxic myoclonus (p. 511.3). Concentrations of endogenous serotonin may be increased through synthesis and serotonin precursors have been given for the treatment of depression (see Oxitriptan, p. 440.3 and Tryptophan, p. 453.2).

Some antidepressants increase serotonin concentrations by inhibiting the metabolism of monoamine oxidase type A, the enzyme that deaminates serotonin. Examples include the older non-selective irreversible inhibitors of monoamine oxidase types A and B (MAOIs) such as phenelzine (p. 442.1), and the newer selective reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (p. 437.2).

Drugs that inhibit the neuronal reuptake of serotonin after release (and thus potentiate its action) are also used in the treatment of depression. They include tricyclic antidepressants such as amitriptyline (p. 401.1), the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (p. 417.1), and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine (p. 454.2). Some SSRIs and SNRIs are also used in the management of anxiety disorders, and SSRIs have been tried in the management of premature ejaculation. Sibutramine (p. 2330.2) is an SNRI used in the management of obesity.

Serotonin receptors, a major site of drug action, are classified by structure and function into seven families: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 with each family having further subtypes. Consequently, drugs acting on serotonin receptors have widely differing chemical structures and diverse pharmacological activities depending on which receptor subtype they act on and whether they act as agonists or antagonists. Serotonin receptor activity is complex and it is possible for the same disorder to be treated by both serotonin agonists or antagonists. For example, serotonin antagonists used in the treatment of migraine include the older ergot-derived compounds such as methysergide (p. 677.1) and metergoline (p. 2557.2) whereas the newer triptans such as sumatriptan (p. 679.2) are selective 5-HT_1 agonists. Buspirone (p. 1042.1) is a 5-HT_{1A} partial agonist used in the treatment of anxiety disorders. Cisapride (p. 1831.3) is a 5-HT_4 agonist used for gastrointestinal disorders. 5-HT_{2C} agonists are under investigation for obesity.

Many different drugs act as serotonin antagonists. They include sedating antihistamines such as carbinoxamine (p. 619.1), cyproheptadine (p. 624.1), methdilazine (p. 635.3), and promethazine (p. 638.2) used for allergic conditions. Some antiserotonergic antihistamines such as cyproheptadine, oxetorone (p. 678.1), and pizotifen (p. 678.2) are also used in the management of migraine. Antagonists specific for the 5-$HT_{2A/2C}$ receptor include the antihypertensive ketanserin (p. 1415.3), the antipsychotic risperidone (p. 1103.2), and the antidepressant trazodone (p. 451.1). The antipsychotic clozapine (p. 1057.3) also has antiserotonergic activity at the 5-$HT_{2A/2C}$ receptor in addition to its other properties. Ondansetron (p. 1872.1) is a 5-HT_3 antagonist used for chemotherapy-induced emesis and postoperative nausea and vomiting.

Drugs with other mechanisms of action involving serotonin systems include fenclonine, an inhibitor of serotonin synthesis that has been used in the treatment of carcinoid syndrome. Reserpine (p. 1485.3) depletes serotonin stores in the brain, heart, and many other organs and has been used in hypertension and psychoses. Fenfluramine (p. 2322.3) and its isomer dexfenfluramine (p. 2320.3) appear to stimulate the release of serotonin and selectively inhibit its reuptake resulting in increased CNS serotonin concentrations; both were formerly used in the treatment of obesity.

Some hallucinogenic drugs of abuse such as bufotenine (p. 2462.2) and lysergide (p. 2547.1) have serotonergic properties.

Serotonin also occurs in stinging nettles (*Urtica dioica*) (p. 2639.3), bananas, and other fruit, and in the stings of wasps and scorpions.

References.

1. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. *Br J Anaesth* 1994; 73: 395–407.
2. Hoyer D, *et al.* International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 1994; 46: 157–203.

Serrapeptase *(rINN)* ⊗

Serrapeptasa; Serrapeptasum; Serrapeptidase; Serratia Extracellular Proteinase; Serratiopeptidasa; Serratiopeptidase; Ceppanemaaa.
CAS — 37312-62-2; 95077-02-4.

Pharmacopoeias. In *Jpn.*

Profile

Serrapeptase is a proteolytic enzyme derived from *Serratia* spp. It has been taken orally for its supposed action in relieving inflammation and oedema associated with conditions such as trauma, infection, respiratory-tract congestion, or chronic venous insufficiency, in usual doses of 5 to 10 mg (10 000 to 20 000 units) up to three times daily.

References.

1. Tachibana M, *et al.* A multi-centre, double-blind study of serrapeptase versus placebo in post-antrotomy buccal swelling. *Pharmatherapeutica* 1984; 3: 526–30.
2. Shimizu H, *et al.* A case of serratiopeptidase-induced subepidermal bullous dermatosis. *Br J Dermatol* 1999; 141: 1139–40.
3. Nakamura S, *et al.* Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease. *Respirology* 2003; 8: 316–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Danzen; *Chile*: Damizen; *China*: Dasen (达先); Qu Tan (曲坦); Seradase (舒瑞达); *Fr.*: Dazen†; *Ger.*: Aniflazym; *Gr.*: Brasan; Enziflur; Eze; Lergan; Retazymon; Revicam; Salavira; Smaritass; Tsoncel; Verolin; *Hong Kong*: Danzen; Unizen; *India*: Adpep; Aldase; Amidase; Asidase; Aslera; Avisera; Bidanzen; Biodase; Biosera; Biosugan-ril; Bradyhist; C-Serra; Cipzen; Copres-M; Cuzen; CYS; Dacnis; Daze; Dazen; Dazina-Forte; Densera; Emanzen; Ensera; Erasan; Eudase; Everser; Flanzen; Flaser Forte; Forses; GS; Infladase Forte; Infladase; Inflazen; Intase; Kineto; Kinex; Lupict; Lyser; Maxilase; Microdase; Optase; Seraim; Serato-M; *Ital.*: Danzen; *Jpn*: Dasen†; *Malaysia*: Danzen; Serrin; Unizen; *Mex.*: Danzen; *Port.*: Aniflazime; *Singapore*: Danzen; Serrazyme; Sinsla†; Tolpa; Unizen; *Thai.*: Dailat; Danzen; Danzinin; Danzyme; Denzo; Fazen; Medizyme; Rodase; Seramed†; Serdas; Serradase; Serrano; Serrao; Serrapep; Serrason; Serrin; Serti-O; Sumidin; Tanza; Unizen; *Ukr.*: Movinaza (Мовиназа); Serox (Серокс).

Multi-ingredient Preparations. *India*: Abdal-SP; AC Sera; ACB-S; Accept-SP; Acec Plus; Aceclo-Sera; Aceclofen; Acedase; Acefen-SP; Aceforce-SP; Acelofan-SP; Acelom-SP; Acemove Plus; Acemove; Acent-SD; Acepara-S; Acetal-SP; Acetuff-SP; Acicloflex-SP; Acimol-S; Aciz-SP; Adocta-P; Aclodase; Aclog-SD; Aclomp-SP; Aclonac-SN; Acloson-SP; Acota-3; Actimol-S; Adifax-SP; Adpep-D; Afesan-SP; Agile-S; Alco-PS; Aldase-D; Aldidase-P; Aldidase; Aleron; Alnase-SP; Alostar-SP; Alto-3D; Amclox-LBS; Amiclox Plus; Amidase-D; Amidase-DP; Amidase-N; Amoxydase; Arflur-3D; Armdic SP; Aroff-EZ; Arrestin-SP; Arsulide-S;

Artidin; Artirox-SP; Asflam; Aslera-D; Aslera-DP; Asonac-SR Plus; Asonac-SR; Atodase-D; Avidox-SP; Aviflox-ST; Avirox-ST; Avisera Plus; Avisera-MR; Axcel-LS; Bclomox; Bilin-CS; Biodase-D; Bionac-Forte; Biopep-D; Biozobid-N; Biozobid; Biplox-SL; C-Serra-D; C-Tri EM; Cadmoxin-CS; Cadpo-D; Cadpo-N; Canmet-SN; Capilac XP; Ceco-SP; Ceflame-K; Ceflame; Celfast Plus; Cep-DP; Cipzen D; Cipzen N; Claridase; Clobee-SP; Clofen-SP; Clonac-SP; Cluster; Cobacta-S; Copres-M-20; Cuga Plus; Cuga; Cure; Cuzen-DP; Cuzen-NM; Cynac-S; Cynac-SP; Cynox; CYS-D; Cytodec Forte; Cytodec; Dacpar-S; Daze-D; Daze-DP; Daze-MX; Dazina-DP; Delaxin; Delnim-SP; Demo-S; Demo-SP; Denim Plus; Densera-D; Densera-N; Devona-S; Dicin; Diciosis; Dicloflam SP; Diclom-SP; Diclopep Plus; Diclopep; Diclosar-P; Dicnacx-S; Dicnacx-SP; Dicol-S; Dicoliv-S; Difin-S; Dikul SP; Dil SE; Dilona-SP; Dilophen-SP; Diplofen 3D; Diser; Divon-S; Dixer-S; Dixfree-SP; Dizer-N; Dofec-S; Dol; Dolocrat; Dolokind-AA; Doloral; Doloroff-ASP; Dolowin Forte; Dordase-D; Dordase-DP; Dox-M ST; DS-15 Plus; DS-15; DSP; Dublace-SP; Ebility; Edase-D; Edase-N; Edilox-S; Emanzen-D; Emanzen-DP; Emanzen-N; Enzoflam; Enzovexx; Erase-D; Essmol-3 Plus; Eudase-D; Eudase-DP; Eudase-MX; Everser-D; Fenbest Plus; Fico-SP; Filco-S; Flago; Flamace-S; Flamace-SP; Flamese; Flanzen-D; Flanzen-DP; Flanzen-MX; Flanzen-RX; Flaser-D; Flaxinac-SP; Flexigesic-S; Flozzen-ST; Flozen Plus; Flozen-AA; Flozen-NS; Flupara-SN; Fonim-S; Forgesic-SP; Fornac-SP; Freedom Forte; Freedom; Genac-SP; Gesnim-S; Gic-SR; Glymox-Plus; Glymox; Godic-S; Gramol-SP; Healpil; Hidiclo Plus; Hidiclodase; Hifenac-D; Himox-LS; Hydase-D; Icobit-S; Inflahit-SP; Inflakod; Inloxy-SLB; Insider; Intase DF; Kevrox-S; Kevrox-SA; Kineto DP; Kineto-D; Kinser-DP; Klick; Klonac-XS; Kurdase Plus; Kurdase-D; Lebec-D; Leemoxin-CS; Leofenac-SP; Litonac-SP; Lyser-A Plus; Lyser-D; Lyser-DP; Mahanac Pro; Mardase-K; Maxiflam-SP; Maxoflam; MDace-SP; Megadase-D; Microdase-D; Microdase-DP; Minipar-SP; Mobinorm-S; Morcet Plus; Movinim-S; Moviz-3D; Moxtid-CS; Moxyplus-SL; Mydic-S; N-S-Plus; Naclomol-S; Nacser D; Neet-S; Nelsid-S; Neomol-XP; Niclofen-S; Niclopar-S; Nifen Plus; Nile-S; Nile-SP; Nimace-SP; Nimdase-P; Nimkul SP; Nimley-S; Nimpain PS; Nimpep; Nimpure-PS; Nimsaid-S; Nimsol Plus; Nimulase-D; Nimulid SP; Nimustar-S; Nimven-S; Nimvon-S; Niser; Nismol-S; Nizapas-SP; Novodase; Novolid-S; Nucoxia-SP; Nugesia-SP; Nusaid-SP; Optase-D; Optizen-D; Orra-D; Orthobid Plus; Oxin Plus; Pacinac; Panama-SP; Panum-SP; Paratel-DS; *Indon.*: Dansera; Flavin; Nutriflam.

Sesame Oil

Aceite de Ajonjolí; Aceite de sésamo refinado; Benne Oil; Gingelly Oil; Oleum Sesami; Refined Sesame Oil; Seesamiöljy; Sésame, huile de; Sesami oleum; Sésamo, aceite de; Sesamolja; Sezamų aliejus; Sezamový olej; Szezámolaj; Teel Oil; Кунжутное Масло; Сезамовое Масло.

CAS — 8008-74-0.

UNII — QX10HYY4QV.

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

Ph. Eur. 8: (Sesame Oil, Refined; Sesami Oleum Raffinatum). The fatty oil obtained from the ripe seeds of *Sesamum indicum* by expression or extraction and subsequent refining. It may contain a suitable antoxidant. It is a clear, light yellow, almost colourless liquid. It solidifies to a soft mass at about -4 degrees. Practically insoluble in alcohol; miscible with petroleum spirit. Store in well-filled, airtight containers. Protect from light. Refined sesame oil for use in the manufacture of parenteral dosage forms should be stored under an inert gas in airtight containers.

USNF 31: (Sesame Oil). The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* (Pedaliaceae). It may contain suitable antoxidants. A pale yellow, practically odourless, oily liquid. 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.

Profile

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps, as well as for culinary purposes. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been seen.

Adverse effects. References to hypersensitivity reactions[1-7] associated with sesame, and subcutaneous nodules[8] after injection of the oil.

1. Kanny G, *et al.* Sesame seed and sesame seed oil contain masked allergens of growing importance. *Allergy* 1996; 51: 952–7.
2. Stern A, Wuthrich B. Non-IgE-mediated anaphylaxis to sesame. *Allergy* 1998; 53: 325–6.
3. Pecquet C, *et al.* Immediate hypersensitivity to sesame in foods and cosmetics. *Contact Dermatitis* 1998; 39: 313.
4. Asero R, *et al.* A case of sesame seed-induced anaphylaxis. *Allergy* 1999; 54: 526–7.
5. Dalal I, *et al.* The pattern of sesame sensitivity among infants and children. *Pediatr Allergy Immunol* 2003; 14: 312–16.
6. Agne PS, *et al.* Sesame seed allergy in children. *Allerg Immunol (Paris)* 2004; 36: 300–305.
7. Gangur V, *et al.* Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol* 2005; 95: 4–11.
8. Darsow U, *et al.* Subcutaneous oleomas induced by self-injection of sesame seed oil for muscle augmentation. *J Am Acad Dermatol* 2000; 42: 292–4.

Uses. References.

1. Ji ZL, *et al.* Therapeutic value of sesame oil in the treatment of adhesive small bowel obstruction. *Am J Surg* 2010; 199: 160–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Rhinaris Nozoil; *India*: Keratex; *Switz.*: Nose Fresh; *UK*: Noseeze.

Multi-ingredient Preparations. *Austral.*: Nozoil; *Canad.*: Pure Gardens; *Ger.*: GeloSitin; *India*: Aloederm-G; Aloederm; *Jpn*: Shiunko; *NZ*: Snorenz; *Singapore*: Snoreeze; *Switz.*: Prevalin; *Turk.*: Snoreless; *UK*: Goodnight StopSnore; Snor-Away.

Shark-liver Oil

Жир Печени Акулы.

UNII — 4B24275HEU.

Profile

Shark-liver oil is the fixed oil extracted from the liver of various species of shark and is used in preparations for anorectal disorders. It has been used as a source of vitamin A.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sperti Preparacion H; *Hung.*: Alkymer; *Pol.*: Ecomer; Selamer†; *Rus.*: Relief Advance (Релиф Адванс); *UK*: Immutone.

Multi-ingredient Preparations. *Arg.*: Sperti PH; *Austria*: Sperti Praparation H; *Canad.*: Preparation H; *Chile*: Sperti Preparation H; *Cz.*: Preparation H; *Gr.*: Preparation H; *Hong Kong*: Preparation H; *Hung.*: Sperti Preparation H; *India*: Medithane; *Irl.*: Preparation H†; *Israel*: Preparation H; *Ital.*: Preparazione H; *Malaysia*: Palmer's Cocoa Butter Formula Scar Serum; *Mex.*: Cartibon; Preparation H; *Neth.*: Sperti Preparation H; *Port.*: Sperti Preparacao H; *Rus.*: Preparation H (Препарейшн Эйч)†; Relief (Релиф); Relief Ultra (Релиф Ультра); *S.Afr.*: Preparation H†; *Singapore*: Preparation H; *Spain*: Preparacion H†; *Switz.*: Sperti Preparation H†; *Thal.*: Preparation H†; *UK*: Preparation H; *Ukr.*: Relief (Релиф); Relief Advance (Релиф Адванс); Relief Ultra (Релиф Ультра); *USA*: Hem-Prep; Preparation H; Rectacaine; Rectagene Medicated Balm; Wyanoids Relief Factor.

Shatavari

Satavar; Satmuli; Wild Asparagus; Шатавари.

NOTE. Distinguish from garden asparagus which is covered in Asparagus, p. 2450.2.

Profile

The root of shatavari, *Asparagus racemosus* (Asparagaceae), is used in Ayurvedic medicine for a range of disorders. There is some interest in its antidiabetic and oestrogenic properties.

The related species *A. adscendens* is used in Ayurvedic medicine as a tonic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Aspamom; Lukure.

Multi-ingredient Preparations. *Hung.*: Munipyrin; *India*: Abana; Addyzoa; Aswal Plus; Cephagraine; Cystone; Diabecon; Bugynin; Evecare; Geriforte; Geriforte; Glowone; Good Time; Gynoset; Happy'tizer†; Herr; Himplasia; Lactacrat; Lactare; Lactare; Lactonic; Lima; Lukol; Memtone; Menosan; Mentofer; *Singapore*: Imunomet; *Ukr.*: Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Fitovit (Фитовит); Imunin (Иммунин)†.

Shepherd's Purse

Bolsa de pastor; Bourse à pasteur; Capsella; Herba Bursae Pastoris; Jaramago; Paniquesillo; Shepherds Purse Herb; Zurrón de pastor; Пастушья Сумка Обыкновенная.

ATC Herb — HG02WC5001 (Capsella bursa-pastoris: herb).

UNII — W0X9457M59 (Capsella bursa-pastoris).

Pharmacopoeias. In *Fr.*

Profile

Shepherd's purse, the aerial parts of *Capsella bursa-pastoris* (*Thlaspi bursa-pastoris*) (Cruciferae) has antihaemorrhagic and astringent properties. It is used to prevent or arrest bleeding, and has been specifically used for menorrhagia. It is also used for urinary-tract disorders and diarrhoea.

Homoeopathy

Shepherd's purse has been used in homoeopathic medicines under the following names: Capsella bursa-pastoris; Thlaspi bursa pastoris; Thlaspi; Capsella; Thal. b. p.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Styprysat.

Multi-ingredient Preparations. *Austral.*: Capsella Complex; Femi-Nan; *Austria*: Menodoron; *Fr.*: Histo-Fluine P; Tisane Provencale no 3†; *Ger.*: Menodoron; *Pol.*: Klimax; Prostapol; Uroprost; *S.Afr.*: Menodoron†; *Switz.*: Menodoron; *UK*: Antitis; Sciargo.

Homoeopathic Preparations. *Canad.*: Renelix; *Chile*: Variplex; *Cz.*: Hormeel S; *Fr.*: Boripharm No 15†; Sabal Serrulata Compose; Urodren; *Hung.*: Hormeel S; *UK*: Menodoron.

Siam Benzoin

Benjoin du Laos; Benjuí de Siam; Bensoe, Siam; Bentsoe, Siam; Benzoe Tonkinensis; Benzoíno derva; Benzoová pryskyřice siamská; Сиамский бензоин.

CAS — 9000-72-0.

ATC Herb — HD02WX5007 (Styrax tonkinensis: resin); HR05WA5054 (Styrax tonkinensis: resin).

UNII — QB299X2IBD.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in some pharmacopoeias under the title benzoin and should not be confused with Sumatra benzoin. *Jpn* and *US* allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 8: (Benzoin, Siam). The resin obtained by incising the trunk of *Styrax tonkinensis*. It has a characteristic odour of vanillin and contains 45.0 to 55.0% of total acids, calculated as benzoic acid, and with reference to the dried drug. Protect from light.

USP 36: (Benzoin). A balsamic resin from *Styrax tonkinensis*, or other species of the *Anthostyrax* section of the genus *Styrax* (Styracaceae). It yields not less than 90% of alcohol-soluble extractive. It occurs as pebble-like tears of variable size and shape, compressed, yellowish-brown to rusty brown externally, milky white on fracture, separate or very slightly agglutinated, hard and brittle at ordinary temperatures but softened by heat. It has an agreeable, balsamic, vanilla-like odour.

Profile

Siam benzoin has been used similarly to Sumatra benzoin (p. 2624.3). It has also been used as a preservative and was formerly used in the preparation of benzoinated lard.

Preparations of Siam benzoin are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Balsolene; Borostyrol; Euvanol; Homeoplasmine; Inotyol; *Israel*: Inotyol.

Homoeopathic Preparations. *Canad.*: Homeoplasmine; *Port.*: Homeoplasmine†; *Switz.*: Homeoplasmine.

Pharmacopoeial Preparations

USP 36: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Siberian Ginseng

Ciwujia; Eleuterokoků šaknys (eleutherococcus); Eleuterokokový kořen (eleutherococcus); Eleuthero; Eleutherococci Radix (eleutherococcus); Eleutherocoque (eleutherococcus); Korzeń eleuterokoka (eleutherococcus); Rysk rot (eleutherococcus); Tajgagyökér (eleutherococcus); Venäläjuuri (eleutherococcus); Элеутерококк; Сибирский Женьшень.

ATC Herb — HN06WA5001 (Eleutherococcus senticosus: root).

UNII — ZX5Z2LW23O (Eleutherococcus senticosus); ZQH6VH092Z (Eleutherococcus senticosus root); 0DAF87OMMD (Eleutherococcus senticosus root water).

NOTE. The name Russian Ginseng has been applied to *Eleutherococcus senticosus*.

The name Ginseng usually refers to *Panax ginseng* and related species (see p. 2513.3).

Some material supplied as Siberian ginseng may be *Periploca sepium* (Asclepiadaceae), a plant unrelated to *Eleutherococcus senticosus*, due to the similarity of the Chinese names for these plants.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *US* also includes a powdered form and a powdered extract.

Ph. Eur. 8: (Eleutherococcus; Eleutherococci Radix). The dried, whole or cut underground organs of *Eleutherococcus senticosus*. It contains not less than 0.08% for the sum of eleutheroside B and eleutheroside E.

USP 36: (Eleuthero). The dried rhizome with roots of *Eleutherococcus senticosus* (Araliaceae) (*Acanthopanax senticosus*) (Araliaceae). It contains not less than 0.08% of the sum of eleutheroside B and eleutheroside E, calculated on the dried basis. Protect from light.

Uses and Administration

Siberian ginseng is reported to enhance natural resistance and to improve performance under stress. It is used similarly to ginseng (*Panax ginseng*) (see p. 2513.3) although the constituents of the two herbs are different. It is also used in traditional Chinese medicine.

Reviews.

1. Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* 2000; 72: 345–93.
2. WHO. Radix Eleutherococci. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/10.html (accessed 04/02/10)

Adverse Effects

Stroke. Thalamic infarction occurred in a 26-year-old man who had taken oral high-energy dietary supplements containing Siberian ginseng daily for about a year during a vigorous training programme for a marathon.[1] He had taken about 1.5 to 2 g of Siberian ginseng daily; small amounts of caffeine were also contained in the preparations. In the absence of other aetiological factors, it was proposed that prolonged daily use of Siberian ginseng and caffeine with vigorous exercise was responsible for the stroke.

1. Polenakovik S. Dietary supplements and stroke. *Mayo Clin Proc* 2005; 80: 1240–1.

Interactions

For a report of raised serum-digoxin concentrations in a patient taking *digoxin* and Siberian ginseng, see Interference with Digoxin Assays, p. 1355.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Russisk Rod; *Ger.*: Eleu-Kokk; Eleu; Konstitutin; *Pol.*: Immunostim†; Syberian; *Switz.*: Vigor; *UK*: Elagen.

Multi-ingredient Preparations. *Arg.*: Sigmafem; Vitalsex; *Austral.*: Aloe Vera Plus; Astragalus Complex; Bacopa Complex; Enhance for Men; For Women Active Woman Formula†; Ginsynergy plus Rhodiola; Mens Dual-Action Multi; Tribulus & Epimedium Compound; Withania Compound; Women's Vitality Multi; Womens Multi; *Fr.*: Ginvit; *Indon.*: Reximax; Tripote†; *Ital.*: Almavigor; Atlantis; Energeia; Fon Wan Memory; Lactovit; Ristabil; Taingel; Vitalmix Fos; *Philipp.*: Immuvit; Jamieson Total Energy; Leginsol-E; *Pol.*: Tripoten; *Rus.*: Arfazetin-E (Арфазетин-Э); Evalar (Эвалар); Kliophyt (Клиофит); Phytonefrol (Фитонефрол); *Spain*: Tonimax; *Swed.*: Chisan; Chisandra; Kan Jang; *Ukr.*: Alfagin (Алфагин); Herbastress (Гербастресс); Immuno-Ton (Імуно-Тон); Liponorm (Липонорм).

Homoeopathic Preparations. *Canad.*: Alfalfa Tonic; Alfalfa Tonic.

Sigetin

Sygethin; Сигетин.

Dipotassium *meso*-3,4-Bis(*p*-sulfophenyl)hexane.

$C_{18}H_{20}O_6S_2K_2$=474.7

CAS — 13517-49-2.

Profile

Sigetin is an analogue of hexestrol (p. 2283.3) but is reported to have no oestrogenic activity. It is used in the management of menopausal symptoms in a usual oral daily dose of 100 to 200 mg.

Sigetin is also reported to enhance the action of oxytocin and to improve placental blood flow and has been given intravenously or intramuscularly in the active management of labour and for threatened intra-uterine fetal asphyxia.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Sagenit (Сагенит).

Silver

Argent; Argentum; E174; Plata; Silber; Серебро.

Ag=107.8682

CAS — 7440-22-4.

ATC — D08AL30.

ATC Vet — QD08AL30.

UNII — 3M4G523W1G.

Profile

Silver is a pure white, malleable and ductile metal. It possesses antibacterial properties and is used topically either as the metal or as silver salts. It is not absorbed to any great extent and the main problem associated with the metal is argyria, a grey discoloration of the tissues (see below). Silver is also present as the core in some copper-wound plastic intra-uterine contraceptive devices. Silver is used as a colouring agent for some types of confectionery.

Salts or compounds of silver that have been used therapeutically include silver acetate (below), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (below), silver-nylon polymers, silver protein (p. 2616.2), and sulfadiazine silver (p. 362.3).

Homoeopathy

Silver has been used in homoeopathic medicines under the following names: Argentum metallicum; Arg. met.

Silver chloride has been used in homoeopathic medicines under the following names: Argentum muriaticum; Arg. mur.

Silver cyanide has been used in homoeopathic compounds under the following names: Argentum cynatum; Argentum cyanatum; Arg cyanat;Arg. cy.

Silver iodide has been used in homoeopathic medicines under the following names: Argentum iodatum; Arg. iod.

Silver oxide has been used in homoeopathic medicines under the following names: Argentum oxydatum; Arg oxyd.

Silver phosphate has been used in homoeopathic medicines under the following names: Argentum phosphoricum; Arg phos.

Reviews.

1. Lansdown AB. Silver in health care: antimicrobial effects and safety in use. *Curr Probl Dermatol* 2006; 33: 17–34.

Argyria. Argyria (generalised argyrosis), characterised by a slate, blue-grey discoloration of the skin, sclera, mucosal surfaces, and nails, developed in a patient who had used vasoconstrictor nasal drops containing silver protein for 4 years. The colour changes were most obvious in skin exposed to the sun. Argyria is irreversible and withdrawal of the nasal drops and use of other measures such as use of sun block and chemical peeling had little effect in this patient.[1]

1. Tomi NS, *et al.* A silver man. *Lancet* 2004; 363: 532.

Catheter care. The benefits of silver coated or impregnated catheters in preventing or reducing urinary-tract infection are uncertain, and studies have provided conflicting evidence. A meta-analysis[1] involving 8 studies with a total of 2355 patients concluded, despite some concerns about the quality and heterogeneity of the studies, that there was a benefit, but that silver alloy coated catheters were significantly more effective in preventing urinary-tract infections than were those coated with silver oxide. A later, slightly larger, meta-analysis[2] also concluded that silver alloy catheters reduced the risk of infection, but considered that a cost-effective analysis was needed.

1. Saint S, *et al.* The efficacy of silver alloy-coated urinary catheters in preventing urinary tract infection: a meta-analysis. *Am J Med* 1998; 105: 236–41.
2. Schumm K, Lam TBL. Types of urethral catheters for management of short-term voiding problems in hospitalised adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 30/06/09).

Wound healing. Silver is incorporated into topical dressings for wound care although a systematic review[1] of 3 randomised controlled studies found insufficient evidence to support the use of silver-containing dressings or other formulations for the treatment of infected or contaminated wounds. Another review[2] concluded that there was insufficient evidence from high-quality studies to justify the routine use of silver dressings in the treatment of uncomplicated leg ulcers or acute wounds, and although there is a slightly better case for use in infected burns, the evidence base is still weak. Bacterial resistance to silver can occur, but this risk can be minimised by choosing dressings that release high levels of silver ions and have a rapid bactericidal action.[3]

The mechanism of bactericidal action of silver in dressings is that silver atoms are oxidised and slowly released as positively charged silver cations when in contact with fluid. The silver ions bind to and disrupt bacterial cell walls as well as binding to bacterial enzymes and DNA. A nanocrystalline silver coating to the dressing increases the surface area of exposure and facilitates release of silver ions. Silver can also be incorporated as complex silver molecules in various different topical formulations that regulate the speed of delivery.[1] Proposed mechanisms of silver resistance have been plasmid acquisition and gene mutation.[3]

1. Vermeulen H, *et al.* Topical silver for treating infected wounds. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 24/06/08).
2. Anonymous. Silver dressings—do they work? *Drug Ther Bull* 2010; 48: 38–42.
3. Chopra I. The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern? *J Antimicrob Chemother* 2007; 59: 587–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Acticoat; *Belg.*: Contreet†; *Fr.*: Atrauman Ag; Urgocell Ag; *Ger.*: Biatain Ag; Contreet†; *Ital.*: Acticoat; Katomed; *Singapore*: Acticoat Flex; Acticoat; *UK*: Acticoat; Avance; Contreet; *USA*: Elta SilverGel; Silverseal; SilvrStat.

Multi-ingredient Preparations. *Arg.*: Actisorb Plus; Efodil; Nova-T; *Belg.*: Aquacel-Ag; Biatain-Ag; *Canad.*: Nova-T; *China*: Nova T (新体); *Fr.*: Actisorb Ag†; Aquacel Ag; Biatain Ag; Micropur Forte DCCNa; Oligorhine; Release Ag†; *Ger.*: Iscador c Arg; Nova-T; SeaSorb-Ag; UrgoCell Silver; Urgosorb Silver; Urgotul Silver; *Hong Kong*: Nova-T†; *Indon.*: Nova-T; *Irl.*: Actisorb Silver; *Israel*: Neocutan Silver; Nova-T; *Ital.*: Actisorb; Aquacel Ag; Katoxyn; Nova-T; Promogran Prisma; Rino Get; Silvercel; Silverdres; Vulnopur; *Malaysia*: Nova-T; *Mex.*: Nova-T; *NZ*: Nova-T†; *S.Afr.*: Nova-T; *Singapore*: Acticoat Absorbent; Nova-T; *Switz.*: Creme vulneraire; Nova-T; *Turk.*: Nova-T†; *UK*: Actisorb Silver; Aquacel Ag; Nova-T; *Venez.*: Nova-T.

Homoeopathic Preparations. *Canad.*: Formula FA 224†; *Cz.*: Galium; *Fr.*: Abbe Chaupitre no 1†; Abbe Chaupitre no 90†; Silicea Complexe No 11; *Ger.*: Agaricus comp Phosphorus; Derivatio H; Derivatio; Weleda Fieber- und Zahnungszapfchen; *Neth.*: Chavita 2.

Silver Acetate

Argenti Acetas; Plata, acetato de; Ацетат Серебра; Уксуснокислое Серебро.

$C_2H_3AgO_2$=166.9

CAS — 563-63-3.

UNII — 19PPS85F9H.

Profile

Silver acetate has been used similarly to silver nitrate as an antiseptic. It has also been used in antismoking preparations.

Smoking cessation. Silver acetate produces an unpleasant taste when combined with cigarettes but a systematic review[1] concluded that there was little evidence that it had any specific effect in promoting smoking cessation. It was considered likely that any effect would be smaller than that produced by nicotine replacement therapy.

1. Lancaster T, Stead LF. Silver acetate for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1997 (accessed 12/04/06).

Silver Nitrate

Argent, nitrate d'; Argenti nitras; Dusičnan stříbrný; Ezüstnitrát; Gümüş Nitrat; Hopeanitraatti; Nitrato de Plata; Nitrato de Prata; Plata, nitrato de; Sidabro nitratas; Silbernitrat; Silvernitrat; Srebra azotan; Нитрат Серебра; Азотнокислое Серебро.

$AgNO_3$=169.9

CAS — 7761-88-8.

ATC — D08AL01.

ATC Vet — QD08AL01.

UNII — 95IT3W8JZE.

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

Ph. Eur. 8: (Silver Nitrate). A white or almost white, crystalline powder or transparent colourless crystals. Very soluble in water; soluble in alcohol. Store in nonmetallic containers. Protect from light.

USP 36: (Silver Nitrate). Colourless or white crystals. On exposure to light in the presence of organic matter, it becomes grey or greyish-black. Soluble 1 in 0.4 of water, 1 in 0.1 of boiling water, 1 in 30 of alcohol, and 1 in 6.5 of boiling alcohol; slightly soluble in ether. Its solutions in water have a pH of about 5.5. Store in airtight containers. Protect from light.

Incompatibility. Silver nitrate is incompatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose

from the reaction of the silver nitrate with alkali released from the glass bottle, which appeared to be soda-glass.[1]

1. PSGB Lab Report P/80/6 1980.

Uses and Administration

Silver nitrate possesses antiseptic properties and is used in many countries as 1% eye drops for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p. 193.2). However, as it can cause irritation, other drugs are often used.

In stick form it has been used as a caustic to destroy warts (p. 1689.3) and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical antiseptics and astringents in other conditions. Instillation of silver nitrate solution has been investigated for pleurodesis in the management of malignant effusions.

Silver nitrate has been used in cosmetics to dye eyebrows and eyelashes.

Homoeopathy

Silver nitrate has been used in homoeopathic medicines under the following names: Argent. Nit.; Argenti nitras; Argentum nitricum; Arg. nit.

References.

1. van Hasselt P, Gudde H. Randomized controlled trial on the treatment of otitis externa with one per cent silver nitrate gel. *J Laryngol Otol* 2004; 118: 93–6.
2. Daliela D, *et al.* Silver nitrate sclerotherapy for 'clinically significant' chyluria: a prospective evaluation of duration of therapy. *Urol Int* 2004; 72: 335–40.
3. da Silveira Paschoalini M, *et al.* Prospective randomized trial of silver nitrate vs talc slurry in pleurodesis for symptomatic malignant pleural effusions. *Chest* 2005; 128: 684–9.
4. Alidaee MR, *et al.* Silver nitrate cautery in aphthous stomatitis: a randomized controlled trial. *Br J Dermatol* 2005; 153: 521–5.
5. Amin M, *et al.* Silver nitrate cauterisation, does concentration matter? *Clin Otolaryngol* 2007; 32: 197–9.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, abdominal pain, diarrhoea, vomiting, coma, and convulsions.

Short-term mild conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria (see Silver, p. 2615.2), which though difficult to treat is mainly a cosmetic hazard.

Although silver nitrate is not readily absorbed, absorption of nitrite after reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Effects on the eyes. Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibacterials and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; 231: 245.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Xin Na Xing (欣纳星); *Pol.*: Mova Nitrat; *Spain*: Argenpal.

Multi-ingredient Preparations. *Austral.*: Nervatona Focus; *Ger.*: Ratanhia comp†; *Neth.*: Diarrheel S; *Switz.*: Wala Echinacea; *UK*: Avoca; *USA*: Grafco.

Homoeopathic Preparations. *Austral.*: Allergy Relief; IBS Eze; Nervatona Focus; *Austria*: Argentum Med Complex; Astomera; Barium Med Complex; Berberis Cosmoplex†; Dalektro; Echinacea-Cosmoplex; Euphorbium Compositum; Gastricumeel; Lakrima; Phosphor-Homaccord; Rhododendroneel; *Canad.*: Arum Triphyllum Plex†; Bladder Irritation; Calnor†; Calsom†; Echinacea Compositum; Endoteel†; Euphorbium Compositum; Euphorbium Compositum; Formula ES 211; Headache & Migraine L77; Headache & Migraine; Homeo-Form CO†; Homeo-Form MI†; Homeo-Form ST†; Infilex†; Kids Calm; Nixotinex; Phosphor-Homaccord†; Stress; Toxex; Travel Sickness; *Chile*: Anacardio con Fosforo; Bioactiv I; Bioactiv V; *Fr.*: Acidum Phosphoricum Compose†; Anxietum; Arum Triphyllum Compose; Boripharm No 10†; Boripharm No 15†; Cocculus Complexe No 73; Conium Complexe No 36†; Gastro-Drainol†; Nux Vomica Compose; Phapax; *Ger.*: EAP-61; Entzundungstropfen; Euphorbium comp SN; Gastro-Pasc; metakaveron; Mucosa compositum; Rufebran gastro†; *Hung.*: Toxex; *Neth.*: Coconium-Gastreu; Euphorbium comp; Gastricumeel; Infragil; Toxex; *Rus.*: Capsicum-Plus (Капсикум-Плюс); *S.Afr.*: Euphorbium Compositum S†; *Switz.*: Akutur; Diarrheel S; Gastricumeel; Gastronol; metaneuron N; Regenaplex Nr. 24b; Regenaplex Nr. 88b; *UK*: Medicinal Gargle; *USA*: Preferred Remedies Antacid.

Pharmacopoeial Preparations

BP 2014: Silver Nitrate Solution; Sterile Silver Nitrate Solution; USP 36: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Silver Protein

Albumosesilber; Argent colloidal (colloidal); Argent Colloïdal par Voie Chimique (colloidal); Argent, protéinate d'; Argentoproteinum; Argentoproteinum Mite (mild); Argentum Colloidale (colloidal); Argentum proteicum; Argentum Proteinicum; Argentum Vitellinicum (mild); Collargol (colloidal); Colloidal Silver (colloidal); Hopea, kolloidinen (colloidal); Hopeaproteiini; Kolloides Silber (colloidal); Mild Protargin (mild); Mild Silver Protein (mild); Mild Silver Proteinate (mild); Plata coloidal (colloidal); Plata, proteína de; Prata Coloidal (colloidal); Protargolum; Proteína de plata fuerte; Proteína de plata ligera (mild); Proteinato de Plata; Proteinato de Prata; Silver, kolloidalt (colloidal); Silver Nucleinate (mild); Silver Proteinate; Silver Vitellin (mild); Silverprotein; Srebra proteinicum; Srebro koloidalne (colloidal); Stříbro koloidní (colloidal); Strong Protargin; Strong Protein Silver; Strong Silver Protein; Vitelinato de Plata (mild); *Vitelinato de Prata (mild); Протарол.*

CAS — 9007-35-6 (colloidal silver); 9015-51-4 (silver protein).

Pharmacopoeias. In *It., Jpn.* and *Viet.*

Eur. (see p. vii) includes Silver, Colloidal, for External Use.

Ph. Eur. 8: (Silver, Colloidal, for External Use; Argentum Colloidale ad Usum Externum). It is colloidal metallic silver, containing protein. It contains 70.0 to 80.0% of Ag, calculated with reference to the dried substance. Green or bluish-black, metallic, hygroscopic, shiny flakes or powder. Freely soluble or soluble in water; practically insoluble in alcohol and in dichloromethane. Store in airtight containers.

Profile

Silver protein solutions have antibacterial properties, due to the presence of the silver, and have been used as eye drops and topically. Various types have been used: the form referred to as silver protein, also sometimes called strong silver protein, contains about 8% silver. Although the mild form contains more silver (about 20%) it is considered to be less active but also less irritating. Colloidal forms of silver protein have a much smaller particle size of silver and may contain up to about 80% silver.

Homoeopathy

Silver protein has been used in homoeopathic medicines under the following names: Argentum colloidale.

Adverse effects. Irreversible neurotoxicity associated with the daily ingestion of a home-made colloidal silver drink for 4 months developed in an elderly patient.[1] He presented with myoclonic status epilepticus, then entered *into a prolonged coma, and eventually died of pneumonia* some months later. On admission, high levels of silver were found in the plasma, erythrocytes, and CSF, and at autopsy there was evidence of selective silver accumulation in the brain. As of October 2007, four reports of silver toxicity in patients ingesting home-made products, likewise prepared using a colloidal silver generator, had also been received by the Australian Adverse Drug Reactions Advisory Committee;[2] one patient also applied it topically after shaving. All patients had high plasma-silver concentrations and developed skin discoloration; some also had systemic symptoms including hepatotoxicity, cardiomyopathy, amnesia, and incoherent speech.

For argyria after prolonged use of nasal drops containing silver protein see under Silver, p. 2615.2.

1. Mirsattari SM, *et al.* Myoclonic status epilepticus following repeated oral ingestion of colloidal silver. *Neurology* 2004; 62: 1408–10.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Dangers associated with chronic ingestion of colloidal silver. *Aust Adverse Drug React Bull* 2007; 26: 19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0710.pdf (accessed 24/06/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Argirol; *Ger.*: Rhinoguttae Argenti diacetylotannici proteinici†; Rhinoguttae pro Infantibus N†; *USA*: RevitaDERM Wound Care.

Multi-ingredient Preparations. *Austria*: Coldargan; *Belg.*: Argyrophedrine†; *Ger.*: Gastrarctin N; *Hung.*: Coldargan†; *Ital.*: Argisone; Argotone Rino; Arscolloid; Bioarscolloid; Corti-Arscolloid; Hyalosilver.

Homoeopathic Preparations. *Fr.*: Argentum Complexe no 98; Kalmia Complexe No 18; Uva Ursi Complexe No 9; *Ger.*: Chirofossat.

Sincalide *(BAN, USAN, rINN)*

CCK-OP; Sincalida; Sincalidum; Sinkalid; Sinkalidi; SQ-19844; Синкалид.

De-1-(S-oxo-L-proline)-de-2-L-glutamine-S-methionine-caerulein.

$C_{49}H_{62}N_{10}O_{16}S_3$=1143.3

CAS — 25126-32-3.

ATC — V04CC03.

ATC Vet — QV04CC03.

UNII — M03GIQ7Z6P.

Pharmacopoeias. *US* includes Sincalide for Injection.

Uses and Administration

Sincalide is the synthetic C-terminal octapeptide of cholecystokinin (see pancreozymin, p. 2582.1) and when given by intravenous injection it stimulates gallbladder *contraction; it also stimulates intestinal muscle.*

Sincalide is used for testing gallbladder function and as an adjunct to cholecystography. It is usually given in doses of 20 nanograms/kg by intravenous injection over 30 to 60 seconds. It is also used as a diagnostic agent, often with secretin (p. 2612.2), for testing the functional capacity of the pancreas; this test generally requires duodenal intubation of the patient and examination of duodenal aspirate. A suggested procedure is to give a 1-hour intravenous infusion of secretin, and 30 minutes after starting this infusion, to start a separate infusion of sincalide 20 nanograms/kg over a 30-minute period. A dose of 40 nanograms/kg may be given to accelerate the transit time of a barium meal through the small bowel; it should be given after the barium meal has passed the proximal jejunum.

Reviews.

1. Prescott WA, Blaiche IF. Sincalide in patients with parenteral nutrition-associated gallbladder disease. *Ann Pharmacother* 2004; 38: 1942–5.

Adverse Effects

Sincalide stimulates gallbladder contraction and gastrointestinal muscle and may give rise to abdominal discomfort. Dizziness, nausea, and flushing may also occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Kinevac; *USA*: Kinevac.

Sivelestat *(USAN, rINN)*

EI-546; LY-544349; ONO-5046; Sivélestat; Sivelestatum; Сивелестат.

*o-(p-*Hydroxybenzenesulfonamido)hippuric acid pivalate.

$C_{20}H_{22}N_2O_7S$=434.5

CAS — 127373-66-4.

UNII — DW162G0P59.

Sivelestat Sodium *(USAN, rINNM)*

Natrii Sivelestatum; Sivelestat sódico; Sivélestat Sodique; Натрий Сивелестат.

$C_{20}H_{21}N_2NaO_7S,4H_2O$=528.5

CAS — 201677-61-4.

UNII — 737RR8Y409.

Profile

Sivelestat is an elastase inhibitor that mainly inhibits neutrophil elastase. It is given by intravenous infusion as the sodium salt in the treatment of acute lung injury associated with systemic inflammatory response syndrome. However, a large study in patients with acute lung injury did not find it of benefit.

References.

1. Zeiher BG, *et al.* Neutrophil elastase and acute lung injury: prospects for sivelestat and other neutrophil elastase inhibitors as therapeutics. *Crit Care Med* 2002; 30 (suppl): S281–S287.
2. Zeiher BG, *et al.* Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. *Crit Care Med* 2004; 32: 1695–1702.
3. Hayakawa M, *et al.* Sivelestat (selective neutrophil elastase inhibitor) improves the mortality rate of sepsis associated with both acute respiratory distress syndrome and disseminated intravascular coagulation patients. *Shock* 2010; 33: 14–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Elaspol.

Skullcap

Escutelaria; Scullcap; Scutellaria; Шлёмник Широколистный.
ATC Herb — HG04BW5035 (Scutellaria lateriflora: herb); HN02BG5013 (Scutellaria lateriflora: herb); HA09WA5022 (Scutellaria lateriflora: herb); HN05CM5025 (Scutellaria lateriflora: herb); HG02WX5004 (Scutellaria lateriflora: herb);
UNII — 7BP4DH5PDC (Scutellaria lateriflora); C6CNB75R61 (scutellaria).

Pharmacopoeias. *Chin.* includes Herba Scutellariae Barbatae (Barbated Skullcap Herb; *Scutellaria barbata*) and Radix Scutellariae (Baical Skullcap Root; *S. baicalensis*).

Eur. (see p. vii) includes Baical Skullcap Root (*S. baicalensis*).

Jpn includes Scutellaria Root (*S. baicalensis*).

Ph. Eur. 8: (Baical Skullcap Root; Scutellariae Baicalensis Radix). The dried, peeled, usually fragmented root of *Scutellaria baicalensis* without rootlets. It is collected in spring or autumn. It contains not less than 9.0% of baicalin ($C_{21}H_{18}O_{11}$ = 446.4) (dried drug). Protect from moisture.

Profile

Skullcap, the aerial parts of *Scutellaria lateriflora* (Labiatae) and other *Scutellaria* spp., has sedative and antispasmodic properties. It is used as a nerve tonic, and for insomnia and menstrual disorders.

Baical skullcap (*S. baicalensis*) is used in Chinese herbal medicine.

References.

1. Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. *Altern Ther Health Med* 2003; 9: 74–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: MEBO; *Pol.*: Baikadent.

Multi-ingredient Preparations. *Austral.*: Albizia Complex; Andrographis Compound; Calmo†; Euphrasia Compound; Feminine Herbal Complex; Herbal Rest & Relax; Masculine Herbal Complex; Nevaton; Nyal Allergy + Hayfever Relief; Nyal Sinus Relief Day + Night; Passionflower Plus†; PulmaCo; Withania Complex; *Canad.*: Calm-Aid†; Herbal Nerve†; Nervrite; Sleep Relax; *Jpn*: Bofutsushosan; Daisaikoto; Gorinsan; Hangeshashinto; Junchoto; Keigairengyoto; Nijutsuto; Nyoshinsan; Orengedokuto; Otsujito; Ryutanshakanto; Saibokuto; Saikanto; Saikokaryukotsuboreito; Saikokeishikankyoto; Saikokeishito; Saikoseikanto; Saireito; Sammotsuogonto; San'oshashinto; Seihaito; Seijobofuto; Seishinrenshiin; Shin'iseihaito; Shosaikoto; Shosaikotokakikyosekko; Unseiin; *Philipp.*: Sleepasil; *Pol.*: Baikaderm; *Singapore*: Bio-Taches Masque†; Bio-Taches†; Disco; *UK*: Herbal Indigestion Naturtabs; HRI Calm Life; Napiers Herbal Stress & Sleep Aid; Neurotone; Newrelax; Nodoff; Quiet Days; Quiet Tyme; Scullcap & Gentian Tablets; St Johnswort Compound; Stressless; Valerian Passiflora and Hops; Vegetable Cough Remover; Wellwoman.

Homoeopathic Preparations. *Austria*: Relax.

Skunk Cabbage

Col apestosa; Dragón fétido; Skunkweed; Симплокарпус Вонючий.
UNII — 5760ZO4B6S (Symplocarpus foetidus); R88254608W (Symplocarpus foetidus root).

Profile

Skunk cabbage, the root and rhizome of *Symplocarpus foetidus* (*Dracontium foetidum*) (Araceae), has expectorant properties and is used in respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Cough Soother Herbal Syrup; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover.

Slippery Elm

Elm Bark; Olmo americano; Olmo resbaladizo; Olmo rojo americano; Slippery Elm Bark; Ulmus; Вяз Ржавый.
ATC Herb — HA02WB5002 (Ulmus rubra: bark).
UNII — 91OY4PXU8Q (Ulmus rubra bark); 63POE2M46Y (Ulmus rubra inner bark).

Pharmacopoeias. In *US*.

USP 36: (Elm). The dried inner bark of *Ulmus rubra* (*U. fulva*) (Ulmaceae). Store in a dry place at a temperature of 8 degrees to 15 degrees.

Profile

Slippery elm contains a considerable amount of mucilage and has been used as a demulcent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Burdock Complex; Cal Alkyline†; Psylli-Mucil Plus†; *Hong Kong*: Vita Coldycin Echinacea Plus†; *UK*: Modern Herbals Pile; Pileabs; Slippery Elm Stomach Tablets.

Homoeopathic Preparations. *Canad.*: Essigen†.

Soapwort

Bouncing Bet; Fuller's Herb; Red Soapwort; Saponaire; Мыльнянка Лекарственная; Мыльная Трава.
ATC Herb — HR05WA5051 (Saponaria officinalis: root);
UNII — 4V1PP5J0HJ (Saponaria officinalis); 3988313MM7 (Saponaria officinalis leaf); RI2K18MA8B (Saponaria officinalis root).

NOTE. Distinguish from White Soapwort, *Gypsophila paniculata* (Caryophyllaceae)

Pharmacopoeias. In *Fr*.

Profile

The root of red soapwort, *Saponaria officinalis* (Caryophyllaceae), contains saponins and is included in herbal preparations for catarrh and other respiratory-tract disorders and for skin disorders. It has been used as a foaming agent. The aerial parts of the herb have also been used.

Homoeopathy

Soapwort has been used in homoeopathic medicines under the following names: Saponaria; Saponaria officinalis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Depuratif Parnel†; *Ger.*: Cefabronchin; *Pol.*: Pectosol; Reumosol; Saponarex; *Port.*: Erpecalm; *Ukr.*: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. *Cz.*: Galium; *Fr.*: Saponaria Compose.

Soda Lime

Cal Sodada; Calcaria absorbens; Calcaria Compositio; Calx Sodica; Chaux Sodée; Натронная Известь.
CAS — 8006-28-8.

Pharmacopoeias. In *Br*. Also in *USNF*.

BP 2014: (Soda Lime). A mixture of sodium hydroxide, or sodium hydroxide and potassium hydroxide, with calcium hydroxide. White or greyish-white granules, or it may be coloured with an indicator to show when its absorptive capacity is exhausted. It absorbs about 20% of its weight of carbon dioxide. Partially soluble in water; almost completely soluble in 1M acetic acid. A suspension in water is strongly alkaline to litmus.

USNF 31: (Soda Lime). A mixture of calcium hydroxide and sodium or potassium hydroxide or both. It may contain an indicator that is inert and that changes colour when the soda lime can no longer absorb carbon dioxide. White or greyish-white granules. May have a colour if an indicator is added.

Incompatibility. Soda lime is incompatible with trichloroethylene.

Profile

Soda lime is used to absorb carbon dioxide, for instance in closed-circuit anaesthetic apparatus, and in the determination of the basal metabolic rate. Limits are specified for particle size, and particles should be free from dust.

Soda lime must not be used with trichloroethylene, since this is decomposed by warm alkali to produce a toxic end product that gives rise to lesions of the nervous system.

Soda lime is irritating and corrosive to skin, mucous membranes, and eyes.

Sodium Aminobenzoate

Aminobenzoate Sodium; Sodium Para-aminobenzoate; Аминобензоат Натрия.
Sodium 4-aminobenzoate.
$C_7H_6NNaO_2$=159.1
UNII — 75UI7QUZ5J.

Pharmacopoeias. In *US*.

USP 36: (Aminobenzoate Sodium). pH of a 5% solution in water is between 8.0 and 9.0.

Profile

Sodium aminobenzoate has been used in analgesic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Potofil; Neo-Ustiol; *Spain*: Tri Hachemina†.

Sodium Arsenate

Arseniato de sodio; Dibasic Sodium Arsenate; Disodium Arsenate; Natrium Arsenicicum; Sodium Arseniate; Мышьяковокислый Натрий; Арсенат Натрия.
$Na_2HAsO_4.7H_2O$=312.0
CAS — 7778-43-0 (anhydrous sodium arsenate); 10048-95-0 (sodium arsenate heptahydrate).
UNII — ANU034TUJ4 (anhydrous sodium arsenate).

Profile

Sodium arsenate was formerly used in the treatment of chronic skin diseases, in parasitic diseases of the blood, and in some forms of anaemia. It has the adverse effects of Arsenic Trioxide, p. 2448.3.

Sodium Camsilate

Sodium Camphorsulphonate; Натрий Камсилат.
Sodium (+)-camphor-10-sulfonate.
$C_{10}H_{15}NaO_4S$=254.3
CAS — 21791-94-6; 34850-66-3.

Pharmacopoeias. In *Viet*.

Profile

Sodium camsilate has been used as a respiratory and cardiac stimulant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Algice; Gripsay; Ozonyl Aquoso; Ozonyl Expectorante; Tetrapulmo†; *Chile*: Gruben; *Ukr.*: Bronchobru (Бронхобрю).

Sodium Carbonate

Sodu węglan.
UNII — 45P3261C7T.

Sodium Carbonate Anhydrous

Carbonato de sodio anhidro; Cenizas de Soda; Cenizas de sosa; E500; Exsiccated Sodium Carbonate; Natrii Carbonas; Natrii Carbonas Anhydricus; Natrio karbonatas, bevandenis; Natrium Carbonicum Calcinatum; Natrium Carbonicum Siccatum; Natriumkarbonaatti, vedetön; Natriumkarbonat, vattenfritt; Sodium (carbonate de) anhydre; Uhličitan sodný; Uhličitan sodný bezvodý; Vízmentes nátrium-karbonát; Безводный Карбонат Натрия.
Na_2CO_3=106.0
CAS — 497-19-8.
UNII — 45P3261C7T.

NOTE. Soda ash is a synonym for the technical grade of sodium carbonate anhydrous.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *USNF* allows the anhydrous substance or the monohydrate.

Ph. Eur. 8: (Sodium Carbonate, Anhydrous). A white or almost white, slightly granular, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

USNF 31: (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Sodium Carbonate Decahydrate

Carbonato de sodio decahidratado; Cristales de Sosa; E500; Natrii Carbonas; Natrii Carbonas Decahydricus; Natrio karbonatas dekahidratas; Natrium Carbonicum Crystal-

lisatum; Natriumcarbonat-Decahydrat; Natriumkarbonaatti-dekahydraatti; Nátrium-karbonát-dekahidrát; Natriumkarbonatdekahydrat; Sodium (carbonate de) décahydraté; Sosa de lavado; Uhličitan sodný dekahydrát; Карбонат Натрия Декагидрат.

$Na_2CO_3.10H_2O$=286.1

CAS — 6132-02-1.

UNII — L5S058G22I.

NOTE. Washing soda is a synonym for the technical grade of sodium carbonate decahydrate.

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

Ph. Eur. 8: (Sodium Carbonate Decahydrate). Colourless, efflorescent, transparent crystals or a white or almost white crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

Sodium Carbonate Monohydrate

Carbonato de sodio monohidratado; E500; Natrii Carbonas Monohydricus; Natrio karbonatas monohidratas; Natriumcarbonat-Monohydrat; Natriumkarbonaattimonohydraatti; Nátrium-karbonát-monohidrát; Natriumkarbonatmonohydrat; Sodium (carbonate de) monohydraté; Sodu węglan jednowodny; Uhličitan sodný monohydrát; Карбонат Натрия Моногидрат.

$Na_2CO_3.H_2O$=124.0

CAS — 5968-11-6.

UNII — 2A1Q1Q3557.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* allows the anhydrous substance or the monohydrate.

Ph. Eur. 8: (Sodium Carbonate Monohydrate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 10% solution in water is strongly alkaline. Store in airtight containers.

USNF 31: (Sodium Carbonate). Colourless crystals, or white, crystalline powder or granules. When exposed to dry air above 50 degrees, it effloresces and at 100 degrees it becomes anhydrous. Soluble 1 in 3 of water and 1 in 1.8 of boiling water.

Profile

Sodium carbonate is used in antacid preparations. Anhydrous sodium carbonate and the monohydrate are also used as reagents. The decahydrate has been used in alkaline baths. Sodium carbonate in its anhydrous or hydrated form is also used as a water softener.

Sodium carbonate may be irritating or mildly corrosive to skin, mucous membranes, and eyes.

Homoeopathy

Sodium carbonate has been used in homoeopathic medicines under the following names: Natrum carbonicum; Natrii carbonas; Natrium carbonicum.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Urologic G.

Multi-ingredient Preparations. *Arg.*: Alikal; Cerosporin; Otocalmia Biotic; Otocerol; Otoclean Gotas Oticas; Sal de Fruta Eno; Sincerum; Uvasal; Yasta; *Austral.*: Eno; *Austria*: Blanel; *Braz.*: Digestbem; Estomazil; Sal de Pruta Eno; Sonrisal; *Canad.*: Lithines du Dr Gustin†; *China*: Shi Wei (仕卫); *Denm.*: Samarin; *Fr.*: Bactident†; Hydralin Classic; *Hong Kong*: Eno†; Hydralin; *Hung.*: Samarin; *India*: Cephagraine; *Irl.*: Cymalon; Resolve†; *Israel*: Urikal; *Ital.*: Gastrotuss; *Port.*: Eno†; Gastropensan†; *S.Afr.*: Pragador†; *Spain*: Sal de Fruta Eno; *Swed.*: Samarin; Samarin; *UK*: Cymalon; Eno; Resolve; *Venez.*: Eno.

Homoeopathic Preparations. *Austria*: Echinacea-Cosmoplex; Spigelon; *Canad.*: Arthritic Pain; Homeo-Form AR†; Spigelon†; *Cz.*: Lamioflur†; *Fr.*: Billerol; Natrum Carbonicum Complexe No 10†; Selenium Complexe No 99; Tamarindus Complexe No 95†; *Ger.*: Entzundungstropfen; *Hung.*: Spigelon; *Switz.*: Lithiumeel; Spigelon; *UK*: Fragador.

Pharmacopoeial Preparations

BPC 1973: Surgical Chlorinated Soda Solution;

USP 36: Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation.

Sodium Chlorate

Clorato de potasio; Natrium Chloricum; Sodii Chloras.

$NaClO_3$=106.4

CAS — 7775-09-9.

UNII — T95DR77GMR.

Profile

Sodium chlorate closely resembles potassium chlorate (p. 2595.2) in its properties and has been used as an astringent. Its main use is as a weedkiller and it is therefore a common household chemical. Poor storage conditions can lead to explosions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Co Bucal.

Sodium Dichloroacetate *(USAN)*

CPC-211; DCA; Dicloroacetato de sodio; Натрий Дихлорацетат.

$C_2HCl_2NaO_2$=150.9

CAS — 2156-56-1 (sodium dichloroacetate); 79-43-6 (dichloroacetic acid).

UNII — 42932X6785.

NOTE. The name Ceresine has been used as a trade mark for sodium dichloroacetate.

Profile

Dichloroacetic acid activates pyruvate dehydrogenase, a mitochondrial enzyme that catalyses metabolism of pyruvate and lactate, and it inhibits glycolysis. It also stimulates myocardial contractility. Sodium dichloroacetate has been used for the treatment of congenital lactic acidosis, lactic acidosis in patients with severe malaria, homozygous familial hypercholesterolaemia, and for severe brain injury. It is also under investigation for stroke. Doses of sodium dichloroacetate for acquired and congenital lactic acidosis are given under Use in Metabolic Acidosis, below.

Administration in children. Doses of sodium dichloroacetate in children are given under Use in Metabolic Acidosis, below.

Adverse effects. Adverse effects reported with sodium dichloroacetate have mainly involved the central and peripheral nervous systems.[1] Anxiolytic or sedative effects are common. Reversible polyneuropathy has been reported after chronic use, as has asymptomatic elevation of serum transaminases. Reduced urate clearance and elevated serum urate levels have been reported in patients with type 2 diabetes mellitus. See also under Use in Metabolic Acidosis, below for references to long-term treatment with sodium dichloroacetate and to early termination of a study due to development of peripheral neuropathy.

1. Stacpoole PW, *et al.* Pharmacokinetics, metabolism, and toxicology of dichloroacetate. *Drug Metab Rev* 1998; 30: 499–539.

Pharmacokinetics. References.

1. Henderson GN, *et al.* Pharmacokinetics of dichloroacetate in adult patients with lactic acidosis. *J Clin Pharmacol* 1997; 37: 416–25.
2. Shangraw RE, Fisher DM. Pharmacokinetics and pharmacodynamics of dichloroacetate in patients with cirrhosis. *Clin Pharmacol Ther* 199966: 380–90.

Use in metabolic acidosis. In a study[1] in 29 patients with lactic acidosis (p. 1775.2), sodium dichloroacetate 50 mg/kg given by intravenous infusion over 30 minutes, followed by a second dose 2 hours after beginning the first infusion, produced a metabolic response in 23 patients with a short-term increase in survival. However, a subsequent study[2] found that, while dichloroacetate infusion did reduce blood-lactate concentrations, it did not alter haemodynamics or survival in patients with severe lactic acidosis. A review[3] of these and other controlled studies in the treatment of acquired and congenital lactic acidosis concluded that the maximum lactate-lowering effect is dose-dependent but independent of time after dosing. Whether lowering lactate levels contributes to reducing morbidity and mortality in hyperlactataemia remains controversial, although data from recent studies suggest that treatment in mild cases may reduce the risk of death. A review[4] of the treatment of children with dichloroacetate for congenital lactic acidosis hypothesised that it might improve quality of life by reducing the frequency of acid–base decompensations, improving neurological function, and stimulating linear growth. A randomised controlled study[5] of dichloroacetate for the treatment of congenital lactic acidosis in 43 patients ranging in age from 3 months to 18 years found that dichloroacetate for 6 months was well tolerated and reduced blood-lactate response to a carbohydrate challenge but had no effect on basal-lactate concentrations nor did it improve neurologic or other measures of clinical outcome. Follow-up[6] of 36 of these children for up to 10 years showed that sodium dichloroacetate is generally well tolerated although it may precipitate or worsen underlying peripheral neuropathy in some cases. In another randomised controlled study[7] of the effects of dichloroacetate in the treatment of the multisystem syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), 13 of 15 patients given the study medication developed peripheral neuropathy, displaying either clinical signs and symptoms or electrophysiological evidence. The study was therefore stopped early, and on this basis, the authors concluded that dichloroacetate could not be recommended for the treatment of MELAS.

In a randomised, double-blind, placebo-controlled study[8] in 124 West African children with severe *Plasmodium falciparum* malaria, a single intravenous infusion of sodium dichloroacetate in a dose of 50 mg/kg given at the same time as quinine increased the rate and magnitude of fall in blood-lactate levels without compromising the plasma kinetics of quinine.

In the UK, the *BNFC* includes the following doses for neonates and children with pyruvate dehydrogenase defects: 12.5 mg/kg 4 times daily orally, adjusted according to response up to 200 mg/kg daily.

Sodium dichloroacetate has also been studied[9] in patients with traumatic brain injury for its lactate-lowering effect in cerebrospinal fluid.

1. Stacpoole PW, *et al.* Dichloroacetate in the treatment of lactic acidosis. *Ann Intern Med* 1988; 108: 58–63.
2. Stacpoole PW, *et al.* A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. *N Engl J Med* 1992; 327: 1564–9.
3. Stacpoole PW, *et al.* Efficacy of dichloroacetate as a lactate-lowering drug. *J Clin Pharmacol* 2003; 43: 683–91.
4. Stacpoole PW, *et al.* Treatment of congenital lactic acidosis with dichloroacetate. *Arch Dis Child* 1997; 77: 535–41.
5. Stacpoole PW, *et al.* Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. *Pediatrics* 2006; 117: 1519–31.
6. Stacpoole PW, *et al.* Evaluation of long-term treatment of children with congenital lactic acidosis with dichloroacetate. Abstract: *Pediatrics* 2008; 121: 1024–5. Full version available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1223.pdf (accessed 25/06/09)
7. Kaufmann P, *et al.* Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology* 2006; 66: 324–30.
8. Agbenyega T, *et al.* Population kinetics, efficacy, and safety of dichloroacetate for lactic acidosis due to severe malaria in children. *J Clin Pharmacol* 2003; 43: 386–96.
9. Williams PJ. Dichloroacetate: population pharmacokinetics with a pharmacodynamic sequential link model. *J Clin Pharmacol* 2001; 41: 259–67.

Sodium Dithionite

Ditionito de sodio; Hidrosulfito de sodio; Natrii Dithionis; Sodium Hydrosulfite; Sodium Hydrosulphite; Sodium Sulphoxylate; Sodu ditionian; Sodu podsiarczyn; Дитионит Натрия.

$Na_2S_2O_4$=174.1

CAS — 7775-14-6.

UNII — 2K5B8F6ES1.

NOTE. The name sodium hydrosulfite is also applied to $NaHSO_2$=88.06.

Pharmacopoeias. In *Pol.*

Profile

Sodium dithionite is used as a reducing agent. It may be used in the form of a simple urine test in the detection of paraquat poisoning. A 0.25% solution has been used to remove phenazopyridine stains from fabric. It is irritant to the skin.

Sodium Gluconate

E576; Gluconato de sodio; Глюконат Натрия.

Monosodium D-gluconate.

$C_6H_{11}NaO_7$=218.1

CAS — 527-07-1.

UNII — R6Q3791S76.

Pharmacopoeias. In *US.*

Profile

Sodium gluconate is a food additive.

Gluconates act as acceptors of hydrogen ions produced by metabolic processes and are an indirect source of bicarbonate ions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ke Rui Te (克瑞特).

Multi-ingredient Preparations. *China*: Er Qi (尔祺); *Ital.*: Altaflora with electrolytes.

Sodium Humate

Гумат Натрий.

CAS — 1415-93-6 (humic acids); 68131-04-4 (sodium humates).

Profile

Humic acids are mixtures of complex macromolecules derived from the decomposition of organic material and are

found in soils and peats. They have been used topically, usually as sodium humate, for musculoskeletal and joint disorders. They also have industrial applications.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Humal; Salhumin; *Ger.*: Salhumin Rheuma-Bad; *Hung.*: Humet-R.

Sodium Hydrogen Sulfate

Sodium Acid Sulphate; Sodium Bisulfate; Sodium Bisulphate.
$NaHSO_4,H_2O$=138.1
CAS — 7681-38-1 (anhydrous sodium hydrogen sulfate); 10034-88-5 (sodium hydrogen sulfate monohydrate).
UNII — BU8V88OWIQ.

Profile

Sodium hydrogen sulfate may be found in preparations used as a buffering agent in gastrointestinal disorders. It has also been used for preparing effervescing baths.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Optacid.

Sodium Hydroxide

Ätznatron; Caustic Soda; Cáustica blanca; E524; Hidrato de sodio; Hidróxido de Sódio; Hidróxido de sodio; Hydroxid sodný; Natrii hydroxidum; Natrio hidroksidas; Natrium Hydricum; Natrium Hydroxydatum; Nátrium-hidroxid; Natriumhydroksidi; Natriumhydroxid; Soda Lye; Sodium hydroxyde de; Sodu wodorotlenek; Sosa cáustica.
NaOH=40.00
CAS — 1310-73-2.
UNII — 55X04QC32I.

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

Ph. Eur. 8: (Sodium Hydroxide). White or almost white, crystalline masses supplied as pellets, sticks, or slabs. It is deliquescent and readily absorbs carbon dioxide. Very soluble in water; freely soluble in alcohol. A 0.01% solution in water has a pH of not less than 11.0. Store in airtight, nonmetallic containers.

USNF 31: (Sodium Hydroxide). White or practically white fused masses, small pellets, flakes, sticks, or other forms. It is hard and brittle and shows a crystalline fracture. When exposed to air it rapidly absorbs moisture and carbon dioxide. Soluble 1 in 1 of water; freely soluble in alcohol. Store in airtight containers.

Uses and Administration

Sodium hydroxide is a powerful caustic. A 2.5% solution in glycerol has been used as a cuticle solvent. An escharotic preparation of sodium hydroxide and calcium oxide was known as London paste. Sodium hydroxide is also used for adjusting the pH of solutions.

Disinfection. For reference to the possible use of sodium hydroxide for the disinfection of material contaminated by the agent causing Creutzfeldt-Jakob disease, see p. 1730.3.

Adverse Effects

Sodium hydroxide is strongly alkaline and corrosive, and rapidly destroys organic tissues.

The ingestion of caustic alkalis causes immediate burning pain in the mouth, throat, substernal region, and epigastrium, and the lining membranes become swollen and detached. There is dysphagia, hypersalivation, vomiting with the vomitus becoming blood-stained, diarrhoea, and shock. In severe cases, abdominal pain, asphyxia due to oedema of the glottis, circulatory failure, oesophageal or gastric perforation, peritonitis, or pneumonia may occur. Stricture of the oesophagus can develop weeks or months later.

Caustic alkalis on contact with the skin can produce full thickness burns leading to extensive damage. Alkali burns to the eyes cause conjunctival oedema and corneal destruction; damage may be irreversible.

Treatment of Adverse Effects

Ingestion should not be treated by lavage or emesis. Dilution with water or milk is generally considered controversial for management of corrosive ingestion. However, early dilution therapy of alkalis may reduce oesophageal injury; large volumes of fluid should be avoided. Neutralisation of alkalis is contra-indicated. The airway should be maintained and shock and pain alleviated.

In cases of skin contamination, clothing should be removed immediately and the skin flooded with copious amounts of water for at least 15 minutes. Excision or skin grafting of burnt areas may be necessary in severe cases. Contaminated eyes should be irrigated thoroughly with water or 0.9% sodium chloride until the conjunctival sac pH is normal, which may require irrigation for up to an hour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Leberinfusion.

Sodium Methylarsinate

Metilarsinato de sodio; Natrium Methylarsonicum; Sodium Metharsinite; Метиларсинат Натрия.
Disodium monomethylarsonate hexahydrate.
$CH_3AsNa_2O_3,6H_2O$=292.0
CAS — 5967-62-4 (sodium methylarsinate); 124-58-3 (methylarsinic acid).

Profile

Sodium methylarsinate is an organic arsenic compound with adverse effects similar to those of arsenic trioxide (p. 2448.3). It was formerly included in some vitamin and mineral preparations. It has also been used as a herbicide.

Sodium Morrhuate *(rINN)*

Morrhuate de Sodium; Morrhuate Sodium; Morruato de sodio; Natrii Morrhuas; Natriummorruaatti; Natriummorruat; Натрия Моррват.
CAS — 8031-09-2.
UNII — 652U49DZTP.

Pharmacopoeias. *Chin.* and *US* include the injection.

Profile

Sodium morrhuate consists of the sodium salts of the fatty acids of cod-liver oil. It is a sclerosant that has been used in the treatment of varicose veins (p. 2564.1). Usual doses are 50 to 100 mg for small or medium veins or 150 to 250 mg for large veins given as a 5% solution by intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Scleromate.

Pharmacopoeial Preparations
USP 36: Morrhuate Sodium Injection.

Sodium Phenylacetate *(USAN)*

Fenilacetato de sodio; Фенилацетат Натрия.
$C_8H_7NaO_2$=158.1
CAS — 114-70-5.
UNII — 48N6U1781G.

Profile

Sodium phenylacetate is used as adjunctive treatment for acute hyperammonaemia (p. 2049.3) and associated encephalopathy in patients with enzymatic deficiencies in the urea cycle. It is given with sodium benzoate (p. 1738.2) as a combined preparation for intravenous infusion in which 1 mL contains 100 mg of each component. The preparation is diluted in sterile glucose injection 10% at ≥25 mL/kg before infusion. Other similar therapies (e.g. oral sodium phenylbutyrate or glycerol phenylbutyrate, see p. 2518.3) should be stopped before starting the infusion. A loading dose is infused over 90 to 120 minutes followed by an equivalent maintenance dose infused over 24 hours. Doses of sodium phenylacetate (given with the same amount of sodium benzoate) are 250 mg/kg for patients weighing 20 kg or less, and 5.5 g/m² for those over 20 kg. Maintenance infusions are continued until plasma ammonia concentrations are normal or oral nutrition and therapy can be tolerated. Sodium phenylacetate has also been given orally.

References.

1. The Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S1–S5.
2. Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr* 2001; **138** (suppl 1): S30–S39.
3. Batshaw ML, *et al.* Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr* 2001; **138** (suppl 1): S46–S55. Correction. *ibid.* 2002; **140**: 490.
4. MacArthur RB, *et al.* Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers. *Mol Genet Metab* 2004; **81** (suppl 1): S67–S73.
5. Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007; **356**: 2282–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Ammonul; Ucephan†.

Sodium Polymetaphosphate

E452; (sodium polyphosphates); Polimetafosfato de sodio; Полифосфат Натрия (sodium polyphosphate).
CAS — 50813-16-6.
UNII — P1BM4ZH95L.

NOTE. Although Sodium hexametaphosphate has been used as a synonym for the polymetaphosphate, the latter also exists in much higher degrees of polymerisation.

Profile

Sodium polymetaphosphate has been used as a 5% dusting powder in hyperhidrosis and bromhidrosis, and as a prophylactic against athlete's foot.

Sodium polymetaphosphate combines with calcium and magnesium ions to form complex soluble compounds and is used as a water softener.

Sodium Pyrophosphate *(USAN)*

Sodu pirofosforan; Tetrasodium Pyrophosphate; TSPP; Пирофосфат Натрия.
$Na_4P_2O_7$=265.9
CAS — 7722-88-5.
UNII — O352864B8Z.

Profile

Sodium pyrophosphate acts as a calcium chelator and is used in products for dental care to reduce tartar formation. It is also used as a food additive, and as a water softener in detergents and for industrial applications. Potassium pyrophosphate (tetrapotassium pyrophosphate) and sodium acid pyrophosphate (disodium pyrophosphate) are used similarly.

Sodium pyrophosphate is also used in kits for the preparation of technetium-99m pyrophosphate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Malvatricin Antitartaro†.

Multi-ingredient Preparations. *Arg.*: Esmedent Dientes Sens Blanq + Ctrol Sarro; Fluordent PX; Sensodyne Antisarro; *Braz.*: Emoform AT; Malvatricin Antiplaca†; Malvatricin Dentes Sensiveis†; *Chile*: FKD; *Fr.*: Fluocaril blancheur†; *Ital.*: AZ Tartar Control; Emoform-Tat; *USA*: Plax.

Sodium Pyruvate

Acetilformiato de sodio; Pirorracemato de sodio; Piruvato de sodio; Пируват Натрия.
Sodium α-ketopropionate; sodium 2-oxopropanoate.
$C_3H_4NaO_3$=111.1
CAS — 127-17-3 (pyruvic acid); 113-24-6 (sodium pyruvate).
UNII — POD38AIF08.

Profile

Sodium pyruvate has been given intravenously in the diagnosis of disorders of pyruvate metabolism.

Relative serum concentrations of lactate and pyruvate after a 10-minute intravenous infusion of sodium pyruvate 500 mg/kg have been used as an aid to the diagnosis of disorders of pyruvate metabolism.[1] Death shortly after pyruvate loading in a 9-year-old child with restrictive cardiomyopathy suggests that the test should not be performed when cardiac function is decreased.[2]

1. Dijkstra U, *et al.* Friedreich's ataxia: intravenous pyruvate load to demonstrate a defect in pyruvate metabolism. *Neurology* 1984; **34**: 1493–7.
2. Matthys D, *et al.* Fatal outcome of pyruvate loading test in child with restrictive cardiomyopathy. *Lancet* 1991; **338**: 1020–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Zitronensaurezyklus-Heel.

Sodium Silicate

Aqua Silicata; Silicato de sodio; Soluble Glass; Vidrio soluble; Water Glass; Натриевосиликатные; Силикат Натрия.

CAS — 1344-09-8.
UNII — UF18F77L3.

Profile

In dry form the most commonly available sodium silicates are Na_2SiO_3, $Na_4Si_2O_7$, and $Na_2Si_3O_7$, with varying amounts of water.Concentrated aqueous solutions of sodium silicate are commercially available and have many industrial uses. The solutions vary in composition, viscosity, and density; the greater the ratio of Na_2O to SiO_2 the more tacky and alkaline the solution.

Sodium Succinate

Succinato de sodio; Янтарнокислый Натрий.
$C_4H_4Na_2O_4.6H_2O$=270.1
CAS — 150-90-3 (anhydrous sodium succinate); 6106-21-4 (sodium succinate hexahydrate).
UNII — V8ZGC8ISR3 (anhydrous sodium succinate); U16QOD6C4E (sodium succinate hexahydrate).

Profile

Sodium succinate, the sodium salt of succinic acid (p. 2214.3), is an ingredient of topical preparations tried for the treatment of cataract. It is also used as a food additive.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Collyre Vitaphakol.

Sodium Tetradecyl Sulfate *(rINN)*

Natrii Tetradecylis Sulfas; Natriumtetradecylsulfat; Natriumtetradekyylisulfaatti; Sodium Tetradecyl Sulphate; Tetradecilsulfato de sodio; Tétradécyl Sulfate de Sodium; Натрия Тетрадецил Сульфат.
Sodium 4-ethyl-1-isobutyloctyl sulfate.
$C_{14}H_{29}NaO_4S$=316.4
CAS — 139-88-8.
ATC — C05BB04.
ATC Vet — QC05BB04.
UNII — Q1SUG5K8D6.

Pharmacopoeias. *Br.* includes as a concentrated form.

BP 2014: (Sodium Tetradecyl Sulfate Concentrate). A clear, colourless gel. Store at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Sodium tetradecyl sulfate is an alkyl sulfate anionic surfactant (p. 2164.1). It has sclerosing properties and is used in the treatment of varicose veins (p. 2564.1). It has also been given in the management of bleeding oesophageal varices (p. 2563.1), and tried in endoscopic injection therapy for nonvariceal bleeding associated with peptic ulcer disease (p. 1813.2).

For sclerotherapy of varicose veins a solution of sodium tetradecyl sulfate is injected slowly into the lumen of an isolated segment of an emptied superficial vein, followed by compression. Solutions are available in a variety of strengths (0.2 to 3%); doses depend on the site and condition being treated. A test dose is advisable in patients with a history of allergy. Facilities for treating anaphylaxis should be available.

Adverse Effects and Precautions

The complications of injection sclerotherapy with sclerosants such as sodium tetradecyl sulfate are discussed under Monoethanolamine Oleate, p. 2564.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fibro-Vein; *Austral.*: Fibro-Vein; *Canad.*: Tromboject; *Fr.*: Trombovar; *Hung.*: Fibro-Vein; *Irl.*: Fibro-Vein; *Israel*: STS†; *Ital.*: Fibro-Vein; Trombovar†; *Neth.*: Trombovar; *NZ*: Fibro-Vein; *Rus.*: Fibro-Vein (ФиброВейн); Trombovar (Тромбовар)†; *S.Afr.*: Fibrovein†; STD†; *Singapore*: Trombovar†; *UK*: Fibrovein; *USA*: Sotradecol.

Pharmacopoeial Preparations
BP 2014: Sodium Tetradecyl Sulphate Injection.

Solidago

Aranyvesszűfű (solidaginis herba); Echtes Goldrutenkraut (*S. virgaurea*); European Goldenrod (*S. virgaurea*); Golden Rod; Goldrutenkraut (*S. gigantea* or *S. canadensis*); Gullris, europeisk (solidaginis virgaureae herba); Gullris (solidaginis herba); Herba Virgaureae (*S. virgaurea*); Kultapiisku, eurooppalainen (solidaginis virgaureae herba); Kultapiisku (solidaginis herba); Naťzlatobýlu obecného (solidaginis virgaureae herba); Paprastųjų rykštenių žolė (solidaginis virgaureae herba); Rykštenių žolė (solidaginis herba); Solidage; Solidage Verge d'Or (*S. virgaurea*); Solidaginis Herba (*S. gigantea* or *S. canadensis*); Solidaginis Virgaureae Herba (*S. virgaurea*); Solidago Virga Aurea (*S. virgaurea*); Verge d'Or; Ziele nawłoci pospolitej (*S. virgaurea*); Ziele nawłoci (*S. virgaurea*); Zlatobýlová nať (solidaginis herba); Золотарник.
ATC Herb — HJ01WB5014 (Solidago virgaurea: *herb*).
UNII — ZHLS62L3PR (Solidago canadensis).

NOTE. The name Aaron's Rod has been applied to several plants including *Solidago* spp., *Verbascum* spp., and *Sempervivum tectorum*.

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

Ph. Eur. 8: (Goldenrod, European; Solidaginis virgaureae herba). The whole or fragmented dried, flowering aerial parts of *Solidago virgaurea*. It contains not less than 0.5% and not more than 1.5% flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) with reference to the dried drug.

Ph. Eur. 8: (Goldenrod; Solidaginis herba). The whole or cut dried, flowering aerial parts of *Solidago gigantea* or *S. canadensis*. It contains not less than 2.5% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4) with reference to the dried drug.

Profile

Solidago virgaurea (Asteraceae) has diuretic and anti-inflammatory activity. It is mainly used in inflammatory disorders of the bladder and kidneys and for the treatment of renal stones. It is also included in herbal preparations used for a variety of disorders.

S. gigantea (Early golden-rod) and *S. canadensis* were once considered to be adulterants of *S. virgaurea* but are now recognised as having similar activity.

Homoeopathy

Solidago has been used in homoeopathic medicines under the following names: Solidago virgaurea; Sol. vir.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Zlatobylova Nat†; *Ger.*: Cystinol Long; Cystium Solidago†; Nephrisol mono†; Nieral; Polbax novo; Solidacur; Solidagoren Mono; Solidagoren mono; Stromic†; Urol; *Hung.*: Stromic.

Multi-ingredient Preparations. *Austral.*: Cranbiotic Super†; Euphrasia Complex; Euphrasia Compound; Extralife Fluid-Care†; Phytodolor; *Austria*: Heumann's Blasen- und Nierentee; Phytodolor; Solubitrat†; Urellum Neu; *Canad.*: Entschlackungstee N†; *Cz.*: Antirevmaticky Caj†; Epilobin; Phytodolor†; Urcyston Planta; *Fr.*: Solution Stago Diluee; Tisane de Sante†; *Ger.*: Aqualibra; BioCyst†; Cefasabal†; Cystinol N; Dr. Scheffler Bergischer Krautertee Blasen- und Nierentee†; Harntee 400 N; Harntee-Steiner†; Heumann Blasen- und Nierentee Solubitrat uro; Nephroselect M; Phytodolor; Prostamed; Renob Blasen- und Nierentee†; Solidagoren; *Hung.*: Herpesil; Prostazyn; Vesevedo; Worishofener; *Ital.*: Flavion; *Malaysia*: Cefasabal; *Pol.*: Diuronis; Fitoven; Nefrobonisol; Nefrol; Nefrosept; NeoFitolizyna†; Prostapol; Reumacor; Urofort; Uromix†; Uroprost; *Rus.*: Prostanorm (Простанорм); *Switz.*: Demonatur Dragees pour les reins et la vessie†; Dragees S pour les reins et la vessie; Impuls dragees pour la vessie et les reins; Impuls pastilles pour les bronches; Nephrosolid; Sabrinin dragees pour les reins et la vessie; Urinex; *Ukr.*: Prostamed (Простамед); Uronephron (Уронефрон).

Homoeopathic Preparations. *Austral.*: Echine†; *Austria*: Berberis Cosmoplex†; *Canad.*: Allergy Relief†; Breathe More; Chelidonium Plex†; Common Mallow Combination†; Drosera Complex; Drosera Plex†; Formula CI 207†; Formula FV 213; Formula Homeo QR 209†; Goldenrod Combination†; Homeoknop Ikoplex 13†; Lymptatox; Male +; Renelix; Sabalia; *Chile*: Ikoplex No 13; *Cz.*: Drosetux; Rhinallergy; *Fr.*: Boripharm No 1†; Boripharm No 41; Chelidonium Compose; Drosera Compose; Drosetux; Formica Rufa Compose; Homeofortil†; Kalium Iodatum Complexe No 84†; L 8; Nux Vomica Compose; Pareira Brava Compose; Rhinallergy; Santaherba; Scrofularia Compose; Thlascose†; Urodren; *Ger.*: Chol-Do; Cysto Hevert; Heparanox H; Hevertner Complex N†; Heweberberol; Hewecyst Blasen-Nieren†; Jsoskleran; Lowe-Komplex Nr 13; metasolidago S†; Nephroplex; Nierentropfen Cosmochema; Phonix Silybum spag; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Renorell; Solidago Hevert Complex; Solidagosan N; Uro Albin; uro-loges; *Hung.*: Drosetux; *Neth.*: Akutur spag; Homeocare Uro; Phonix Solidago comp; Reneel H; Restructa H; *Rus.*: Psorilom (Псорилом); *Switz.*: Akutur; Drosetux; Rhinallergy; Silacten; *Ukr.*: Homviocorin-N (Хомвиокорин-N); *USA*: Preferred Remedies Antacid; Preferred Remedies Detoxin.

Sorrel

Acedera Común; Azeda-Brava; Garden Sorrel; Herba Rumicis Acetosae; Oseille; Sorrel; Dock; Sour Dock; Vinagrera; Wiesensauerampfer; Щавель Обыкновенный (*Rumex acetosa*); Щавель Кислый (*Rumex acetosa*).

NOTE. The name sour dock has also been used for yellow dock (p. 2649.3).

Profile

Sorrel (*Rumex acetosa*, Polygonaceae) has been used for respiratory-tract disorders. It is also used as a culinary herb.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Sinupret; *Austria*: Sinupret; Solvopret†; *Cz.*: Sinupret; *Ger.*: Sinupret; *Hong Kong*: Sinupret; *Hung.*: Sinupret; *Indon.*: Sinupret†; *Malaysia*: Sinupret; *Mex.*: Bisolsinus; *Philipp.*: Sinupret; *Pol.*: Sinupret; *Rus.*: Sinupret (Синупрет); *Singapore*: Sinupret; *Swed.*: Sinova; *Switz.*: Sinupret; *Thai.*: Sinupret†; *UK*: Sinueeze; Sinuherb; *Ukr.*: Sinupret (Синупрет).

Homoeopathic Preparations. *Canad.*: Essigen†.

Soya Isoflavones

Соевые Изофлавоны.

Pharmacopoeias. In *US*.

USP 36: (Powdered Soy Isoflavones Extract). It is prepared from the seeds of *Glycine max* (Fabaceae) by extraction with water or hydroalcoholic mixtures. Its content is calculated on the dried basis as the sum of daidzin, glycitin, genistin, and one or more of the following isoflavones: malonyl daidzin, malonyl glycitin, malonyl genistin, acetyl daidzin, acetyl glycitin, acetyl genistin, daidzein, glycitein, and genistein. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Daidzein

Даидзеин.
4′,7-Dihydroxyisoflavone; 7-Hydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_4$=254.2
CAS — 486-66-8.
UNII — 6287WCSJ2L.

Genistein

CI-75610; Genisteol; Prunetol; Генистеин.
4′,5,7-Trihydroxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one.
$C_{15}H_{10}O_5$=270.2
CAS — 446-72-0.
UNII — DH2M523P0H.

Profile

Genistein and daidzein are soya isoflavones. Genistein, a tyrosine kinase inhibitor, is a phytoestrogen that is used for the relief of menopausal symptoms. It is also being investigated for its beneficial effect on blood lipids and for its proposed tumour-suppressing activity. Daidzein has been used similarly. Daidzein, mainly in the form of its glycoside daidzin, is a component of some herbal medicines traditionally used in the management of alcohol abuse.

DT56a, a phytoestrogen derived from soya, is also used for the relief of symptoms associated with menopausal disorders.

Effects on the endocrine system. For a suggestion that isoflavones in soya-based formulas may exert biological effects, see p. 2093.3.

Hyperlipidaemias. For a discussion of possible beneficial effects of soya isoflavones on blood lipids, see p. 2093.2.

Menopausal disorders. Soya contains phytoestrogens in the form of isoflavones, in particular daidzein (above) and genistein (above), which have been investigated for their oestrogen-modulating effects in the treatment of menopausal symptoms (p. 2245.1).[1] It is thought that genistein may exert oestrogenic effects in the presence of low oestrogen concentrations, but that it may be anti-oestrogenic when concentrations of oestrogen are high.[2]

A small reduction in the incidence of hot flushes has been noted with soya isoflavone extract.[3] A systematic review,[4] however, concluded that phytoestrogens available as soya foods, soya extracts, or red clover extracts (p. 2482.1) do not improve hot flushes or other menopausal symptoms.

Isoflavones may have a beneficial effect on cholesterol and lipid concentrations (see Hyperlipidaemias, p. 2093.2). Some epidemiological studies and *animal* data suggest that they may also provide protection against breast cancer.[1,2,5] However, phytoestrogens could also stimulate breast tumour growth due to oestrogenic activity.[6] These stimulating and inhibitory effects may be concentration-dependent; soya products contain only small amounts of phytoestrogens and it may be difficult to consume enough soy to have any beneficial effect on breast cancer growth.[7] A meta-analysis[8] concluded that soya intake may be associated with a small reduction in breast cancer risk, but that this result should be interpreted with caution due to confounding factors and a lack of dose response. Given the possibility of adverse effects, recommendations for high-dose soya isoflavone supplementation to prevent breast cancer or its recurrence are premature.

A few small studies have shown that soya isoflavones can decrease bone turnover, leading to speculation that they could be used to prevent osteoporosis (p. 1168.1).[1] The effects of these isoflavones should be investigated in larger studies before they can be recommended as alternatives to conventional HRT.[5-7] (For the view that they may lack cardiovascular benefits see Hyperlipidaemias, p. 2093.2.) In a study to investigate effects on cognitive function, bone mineral density, and plasma lipids in postmenopausal women, no differences were noted between soya protein containing isoflavones, and placebo.[9]

1. Vincent A, Fitzpatrick LA. *Soy isoflavones: are they useful in menopause? Mayo Clin Proc* 2000; 75: 1174–84.
2. Goldwyn S, *et al.* Promotion of health by soy isoflavones: efficacy, benefit and safety concerns. *Drug Metabol Drug Interact* 2000; 17: 261–89.
3. Upmalis DH, *et al.* Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2000; 7: 236–42. Correction. *Ibid.*: 422.
4. Krebs EE, *et al.* Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstet Gynecol* 2004; 104: 824–36.
5. Sirtori CR. Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symptoms and osteoporosis. *Drug Safety* 2001; 24: 665–82.
6. Mason P. Isoflavones. *Pharm J* 2001; 266: 16–19.
7. de Lemos ML. Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother* 2001; 35: 1118–21.
8. Trock BJ, *et al.* Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 2006; 98: 459–71.
9. Kreijkamp-Kaspers S, *et al.* Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004; 292: 65–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Isolife; Melinda; Sojadiol; Sojar Men; Tanvimil Isoflavonas; *Belg.*: Elugyn; *Braz.*: Buona; Flavonil†; Isoflavine; Menop; Soy 50; Soyfemme; *Chile*: Fitoflavona; Phyto Soya; *Fr.*: Gydrelle Phyto; Inoclim; *Hong Kong*: Phyto Soya; Phyto-Care; *India*: Isoflav; Menoflav; *Indon.*: Calvonin; Promensil; *Ital.*: Genivis; Soymen Gel; *S.Afr.*: Phytopause†; *Singapore*: Isoflav; Isovon; Phyto Soya; *Spain*: Flavosul; *Swed.*: Menosoy; *Thai.*: Flamina; *Turk.*: Gynogen; Isoflavin; *Venez.*: Climasoy.

Multi-ingredient Preparations. *Arg.*: Equilibrol Fem; Fem Plus 50; Fitogenos; Isaflavon; La Edad De Oro; Melinda Plus; Selder; Sigmafem Free; Sigmaflavon Plus; Snella D + E; Sojar Plus-Calcio; Tanvimil Gel; Tanvimil Isoflavonas Caclcio D3; Tanvimil Isoflavonas; Upsala; *Austral.*: In-Control; Meno Support Plus; *Canad.*: Natural HRT; Phytoestrin; *Chile*: Dennov; *Fin.*: Femarelle; *Fr.*: Anacaps†; Estrofort†; Imedeen Prime Renewal†; Menoceane†; *Gr.*: Femarelle; *Hong Kong*: Caltrate + Soy†; Femarelle; Palmetto Plus†; Phyto-Ease; Phytoestrin†; *India*: Alfaflavon; Calciflavone; Cavit-PM; Ease-PMS; Estovon-XT; Estovon; Evepearl-MP; Femarelle; Gynacea; Isovon; Melaglow; Menoease; Menopace Iso; Menosoft; Menosoy; Moxafav; Osteo-G; *Indon.*: Biocal-95; Bonilav; Cal-95; Calosbon; Calplex; Femosa; Hi-Bone; Isofem†; Isomenopace; Naturliver; Opus; Ossovit Plus; *Israel*: Femarelle†; *Ital.*: Apogeo; Biolastic T5; Climil Complex; Climil Gel; Climil-80; Evestrel; Fitogenase; Ginepausil; Rinnova; *Malaysia*: Isoflav; Shine Fememino; *Mex.*: Caflovan; Tofupill; *Norw.*: Femarelle; *S.Afr.*: Phytopause BSF†; *Singapore*: Caltrate + Soy†; Femarelle; Palmetto Plus†; Phytoestrin†; *Spain*: Femarelle; *Swed.*: Femarelle; *UK*: Aria; Estroven Nighttime; Estroven; Femarelle; SoyPlus; *USA*: Better Cholesterol; Femarelle; Posteum; *Venez.*: Calcibon D Soya.

Pharmacopoeial Preparations

USP 36: Soy Isoflavones Capsules; Soy Isoflavones Tablets.

Sparteine Sulfate *(USAN, rINN)*

Esparteína sulfato de; Spart. Sulph; Sparteine, Sulfate de; Sparteine Sulphate; Sparteine Sulphate; (-)-Sparteine Sulphate; Sparteini Sulfas; Sparteinum Sulfuricum; Sulfato de esparteína; Спартеина Сульфат.

Dodecahydro-7,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1′,2′-*e*][1,5]diazocine sulphate pentahydrate.

$C_{15}H_{26}N_2,SO_4,5H_2O$=422.5

CAS — 90-39-1 (sparteine); 299-39-8 (anhydrous sparteine sulfate); 6160-12-9 (sparteine sulfate pentahydrate).

ATC — C01BA04.

ATC Vet — QC01BA04.

UNII — GQ3J2TLZ7E.

Pharmacopoeias. In *Fr.* and *Viet.*

Profile

Sparteine sulfate is a salt of the dibasic alkaloid, sparteine, which is obtained from scoparium (p. 2611.3). Sparteine sulfate has been reported to lessen the irritability and conductivity of cardiac muscle and has been used in the treatment of cardiac arrhythmias. Small doses stimulate and large doses paralyse the autonomic ganglia. Peripherally, it has a fairly strong curare-like action, arresting respiration by paralysing the phrenic endings.

The metabolic oxidation of sparteine exhibits genetic polymorphism and this property has been exploited in *in-vitro* screening tests to identify other drugs that may be subject to similar genetic variations in their metabolism.

Precautions. Sparteine present in a herbal slimming preparation might cause adverse effects in slow metabolisers if excessive doses were ingested; pregnant women might be particularly at risk.[1]

1. Galloway JH, *et al.* Potentially hazardous compound in a herbal slimming remedy. *Lancet* 1992; 340: 179.

Spearmint

Asanda; Grüne Minze; Hierba buena; Menta; Menta crespa; Menta romana; Menta verde; Mentastro verde; Mentha Viridis; Menthae Crispae Folium; Menthe douce; Menthe verte; Mint; Sándalo de jardín; Speer-Minze; Мята Колосистая (*Mentha spicata*); Yerba buena; Yerba santa; Yerbabuena.

UNII — J7I2T6IV1N (spearmint); FV98Z8GITP (mint); O2H83I4PUN (Mentha spicata).

Profile

Spearmint consists of the dried leaves and flowering tops of common spearmint, *Mentha spicata* (*M. viridis*) or of scotch spearmint (*M. cardiaca*) (Labiatae). Spearmint is the source of spearmint oil (below). It has carminative properties and is used as a flavour.

References.

1. Akdoğan M, *et al.* Effect of spearmint (*Mentha spicata* Labiatae) tea on androgen levels in women with hirsutism. *Phytother Res* 2007; 21: 444–7.
2. Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytother Res* 2010; 24: 186–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Glamebil.

Multi-ingredient Preparations. *Canad.*: Calmane; *Chile*: Te Laxante†; *Fr.*: Detoxifiance; Tisane Provencale no 4†; *Indon.*: Fitajoint; *Switz.*: Kernosan Eau Dentifrice†; Tisane antirhumatismale; Tisane pour l'estomac; Tisane pour le coeur et la circulation; Tisane pour le sommeil et les nerfs; *Ukr.*: Florised (Флорисед).

Spearmint Oil

Huile Essentielle de Menthe Crépue; Menta, aceite esencial de; Oleum Menthae Crispae; Oleum Menthae Viridis; Мятное Масло.

UNII — C3M81465G5.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Spearmint Oil). It is obtained by distillation from fresh flowering plants of *Mentha spicata* or *Mentha X cardiaca*. A clear colourless, pale yellow or greenish-yellow liquid when freshly distilled, visibly free from water and with the odour of spearmint. It becomes darker and viscous on keeping. It contains not less than 55% w/w of carvone. Soluble 1 in 1 of alcohol (80%) at 20 degrees; the solution may become cloudy when diluted. Store at a temperature not exceeding 25 degrees in well-filled containers. Protect from light.

Uses and Administration

Spearmint oil has similar properties to peppermint oil (p. 1877.1) and is used as a carminative and as a flavour. It is also used in aromatherapy.

Adverse Effects

Hypersensitivity. Allergic contact cheilitis in a patient has been attributed to the spearmint oil present in tooth paste.[1] Other cases of sensitivity reactions have been reported.[2,3]

1. Skrebova N, *et al.* Allergic contact cheilitis from spearmint oil. *Contact Dermatitis* 1998; 39: 35.
2. Bonamonte D, *et al.* Allergic contact dermatitis from Mentha spicata (spearmint). *Contact Dermatitis* 2001; 45: 298.
3. Clayton R, Orton D. Contact allergy to spearmint oil in a patient with oral lichen planus. *Contact Dermatitis* 2004; 51: 314–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Pervinox Extra Mint; *Austria*: Euka; *Chile*: Polvos Alcalinos; *Hung.*: Pudin Haran; *India*: Aglotus; *Indon.*: Listerine Coolmint†; *Ital.*: Dentosan Azione Intensiva; Dentosan Mese; *Philipp.*: CleanEars; Listerine Coolmint; Medisnore; *Switz.*: Alvogyl; *UK*: Fre-bre; Profelan; *USA*: Nostrilla Conditioning Double Moisture.

Spigelia Anthelmia

Demerara Pinkroot; Erva-lombrigueira; Pink Root of Demerara; West Indian Pinkroot; West Indian-pink; Wormbush.

UNII — WYT05213GE.

NOTE. The names Indian Pink, Pink Root (or Pinkroot), and Worm Grass (or Wormgrass) have been applied to both Spigelia Anthelmia and Spigelia Marilandica.

Spigelia Marilandica

American Wormgrass; American-wormroot; Carolina Pink; Carolina Wormroot; Maryland Pink; Maryland Pinkroot; Maryland Wormroot; Maryland-Wormroot; Star Bloom; Starbloom; Woodland Pinkroot; Spigelia.

UNII — F1A4U61CP (Spigelia marilandica); *467D26HS08* (Spigelia marilandica root).

Profile

The dried roots and rhizomes of *Spigelia anthelmia* and *S. marilandica* (*Lonicera marilandica*), (Loganiaceae) have historically been used in herbal and traditional medicine for the treatment of intestinal helminth infections and for cardiac disorders. The entire plant has also been used. Adverse effects, which are reportedly less frequent if given with a purgative, include dizziness, visual disturbances, and muscle spasms. High doses may result in cardiotoxicity, convulsions, and respiratory depression; fatalities have occurred. *S. anthelmia* may be more potent and more toxic than *S. marilandica*.

Homoeopathy

Spigelia has been used in homoeopathic medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Port.*: Cephyl†.

Homoeopathic Preparations. *Austria*: Cactus compositum; Cora; Cralonin; Spigelon; *Canad.*: Formula DM 210†; Sinusalia; Spigelon†; *Fr.*: Abbe Chaupitre no 20†; Amanita Complexe No 75; Boripharm No 31; Cina Compose; Neurocynesine†; Sclero-Drainol†; *Ger.*: Cardioselect N; Confludin N; Cralonin; Craniocyl Ho-Len-Complex; DolorA; Habstal-Cor N; HanoCor N; Migrane Hevert†; Migrane-Gastreu R16; Myonasan; Pectapas CPL; Pectapas SL; Pectapas; Rephalgin N; Strophanthus comp; *Hung.*: Spigelon; *Neth.*: Cephalite; Cralonin H; Cralonin; Neurocynesine†; *Switz.*: Cralonin; Spigelon.

Spike Lavender

Lavande aspic; Лаванда Широколистная.

Profile

Spike lavender, *Lavandula latifolia* (Lamiaceae), is used similarly to lavender (p. 2541.1) as a sedative and for biliary disorders. It is the source of spike lavender oil (below).

Spike Lavender Oil

Alhucema, aceite esencial de; Huile Essentielle d'Aspic; Oil Lavand. Spic.; Oleum Lavandulae Spicatae; Speiköl; Spicae Actheroleum; Spike Oil; Спиковое Лавандовое Масло.

UNII — 752HYV1VJQ.

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

Ph. Eur. 8: (Spike Lavender Oil; Spicae Aetheroleum). The essential oil obtained by steam distillation of the flowering tops of *Lavandula latifolia*. A clear, mobile, light yellow or greenish-yellow liquid with an odour reminiscent of cineole

and camphor. Store at a temperature not exceeding 25 degrees.

Profile

Spike lavender oil is the volatile oil from *Lavandula latifolia* (Labiatae). It resembles lavender oil (p. 2541.1) in its properties and is mainly used in perfumery. It is also used in aromatherapy. Hypersensitivity reactions may occur.

Preparations

Proprietary Preparations (details are given in Volume B).

Single-ingredient Preparations. *Austria*: Tavipec; *Thai.*: Tavipec.

Multi-ingredient Preparations. *Austria*: Novipec†; Tussamag; *Rus.*: Carmolis (Кармолис); *S.Afr.*: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Stuidruppels; *Switz.*: Baume du Chalet; Fortalis.

Spirulina

Espirulina; Спирулина.

Profile

Spirulina is a species of blue-green algae that has been promoted as an anorectic, but there is no convincing evidence that it is safe or effective for this indication.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Eufit; Fitness; Novalina; Nuclina; *Indon.*: Spirumate†; *Rus.*: Radahlorin (Радахлорин); *UK*: Biolina; Immulina.

Multi-ingredient Preparations. *Arg.*: Adel; Centella Asiatica Spir; Doctor 10 Body; No-Gras; Spiruvita; *Austral.*: Cal Alkyline†; NutriMulti; *Chile*: Natur-Zin; Natursel-C; Perfect Body; Reducform-F; *Fr.*: Biofirm; Cicatendon; Proselem; Ultraselem; *India*: Actima; Ampiro; Antex; Antoxyl; Becose; Bethadoxin-XL; Candor; Fezys-SM; MSA; Neuroage Plus; Newvit-S; Optifit; Oximino; Vitexid; *Ital.*: Lactovit; Salovit; *Philipp.*: Spigrow for Boys; Spigrow for Girls; *USA*: Alive Once Daily Womens 50+ Ultra Potency.

Star Anise

Anís Estrellado; Anis Étoilé; Anisi Stellati Fructus; Anisum Badium; Anisum Stellatum; Badiana; Badiane; Badiane de Chine; Badyáníkový plod; Chinese Star Anise; Csillagánizs; Owoc anyżu gwiaździstego; Star Anise Fruit; Sternanis; Stjärnanis; Tähtianis; Žvaigždanyžių vaisiai; Анис звёздчатый.
*UNII — XKC1657P78 (*Illicium verum *seed); CK15HA8438 (*Illicium verum *fruit).*

NOTE. Distinguish from Japanese star anise.

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

Ph. Eur. 8: (Star Anise; Anisi Stellati Fructus). The dried composite fruit of *Illicium verum*, containing not less than 7% v/w of essential oil with reference to the anhydrous drug and a minimum 86.0% of *trans*-anethole in the essential oil. Protect from light.

Uses and Administration

The fruit of star anise, *Illicium verum* (Illiciaceae), is used as an expectorant for catarrh and as a gastrointestinal antispasmodic. It is used with thyme (p. 2630.2) in herbal preparations for colds and upper respiratory-tract disorders. It is also used as a culinary spice.

Star anise is the source of star anise oil (below). It is also the source of shikimic acid, which is used in the production of the anti-influenza drug oseltamivir (p. 1006.2).

Adulteration of star anise with Japanese star anise (shikimi fruits; *I. anisatum*) has been responsible for cases of neurotoxicity (see below). Import restrictions have been implemented in the EU. The problem is further complicated because the name *I. anisatum* has been applied to *I. verum*.

Adverse Effects

Effects on the nervous system. Neurotoxicity has been associated with the use of star anise infusions in infants.[1-4] The toxicity is attributed to adulteration or contamination of Chinese star anise (*Illicium verum*) with Japanese star anise (*I. anisatum*), which contains toxic sesquiterpene lactones such as anisatin.

1. Garzo Fernandez C, *et al.* Casos de enfermedad de sintomatología neurológica asociados al consumo de anís estrellado empleado como carminativo. *An Esp Pediatr* 2002; 57: 290–4.
2. Minodier P, *et al.* Intoxication aiguë par la badiane chez Le nourrisson. *Arch Pediatr* 2003; 10: 619–21.
3. Ize-Ludlow D, *et al.* Neurotoxicities in infants seen with the consumption of star anise tea. Abstract: *Pediatrics* 2004; 114: 1330. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/5/e653.pdf (accessed 16/08/10)
4. de la Rubia Fernández L, *et al.* Intoxicación por anís estrellado. *An Pediatr (Barc)* 2009; 71: 381–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Wunderbalsam; *Austria*: Pervivo; *Braz.*: Ductoveran; *Ger.*: Cefabronchin; *Hung.*: Bittner; *Ital.*: Relaxcol; *Pol.*: Pervivo; *Switz.*: Kernosan Eau Dentifrice†; Tisane laxative; Tisane pectorale et antitussive; *Venez.*: Atrobel; Ervossil.

Homoeopathic Preparations. *Austria*: Tartephedreel.

Star Anise Oil

Anisi Stellati Aetheroleum; Anisi Stellati Etheroleum; Badiane, huile essentielle de; Badyáníková silice; Oleum Badianae; Sternanisöl; Stjärnanisolja; Tähtianisöljy; Žvaigždanyžių eterinis aliejus; Бадьяновое Масло.
UNII — 6RXP35EIRE.

Pharmacopoeias. In *Eur.* (see p. vii). *USNF* includes star anise oil under the title Anise Oil.

Ph. Eur. 8: (Star Anise Oil; Anisi Stellati Aetheroleum). An essential oil obtained by steam distillation from the dry ripe fruits of *Illicium verum*. It contains 0.2 to 2.5% linalol, 0.5 to 6.0% estragole, less than 0.3% α-terpineol, 0.1 to 0.5% *cis*-anethole, 86 to 93% *trans*-anethole, 0.1 to 0.5% anisaldehyde, and 0.1 to 3.0% foeniculin. A clear, colourless or pale yellow liquid. Relative density 0.979 to 0.985. F.p. 15 degrees to 19 degrees. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

USNF 31: (Anise Oil). The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* (Apiaceae) or from the dried ripe fruit of *Illicium verum* (Illiaceae). Congealing temperature not lower than 15 degrees. Soluble 1 in 3 of alcohol (90%). Store in well-filled airtight containers. If solid material has separated, carefully warm the oil until it is completely liquefied, and mix before using.

Profile

Star anise oil is included in preparations for the treatment of coughs and cold symptoms. It is used in the pharmaceutical and food industries as an alternative to anise oil (see p. 2444.3). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Zap.

Multi-ingredient Preparations. *Cz.*: Biotussil; *Ger.*: Makatussin *Tropfen*; *Swed.*: Alpenkraft; Multipretten; *Switz.*: DUL-X warm; DUL-X; Liberol Baby N; Odontal; *Turk.*: Sandolin†.

Pharmacopoeial Preparations
BP 2014: Camphorated Opium Tincture; Compound Orange Spirit; Concentrated Anise Water; Concentrated Camphorated Opium Tincture.

Stone Root

Collinsonia; Collinsonia del Canadá; Hardhack; Heal-all; Knob Root; Коллинсония Канадская (*Collinsonia canadensis*).
*UNII — J98TD5377V (collinsonia); O2630F3XDR (*Collinsonia canadensis *root).*

Profile

Stone root, the root and rhizome of *Collinsonia canadensis* (Labiatae), has diuretic and litholytic properties and is used in the treatment of renal and urinary calculi. It is also used as an astringent for gastrointestinal disorders. It has also been included in herbal preparations for haemorrhoids.

Homoeopathy

Stone root has been used in homoeopathic medicines under the following names: Collinsonia; Collinsonia canadensis; Collin. c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Diuretic Tablets; *UK*: Piletabs.

Homoeopathic Preparations. *Canad.*: Hae 2 Complex†; *Fr.*: Aesculus Complexe No 103; Carominthe; Sepia Compose; *Ger.*: Haemorrhoid-Gastreu N; *Neth.*: Collite; *Switz.*: Hemolingual.

Storax

Balsamum Styrax Liquidus; Estoraque; Estoraque Líquido; Liquid Storax; Styrax; Стиракс.
*ATC Herb — HD03WX5010 (*Liquidambar styraciflua: *balsam); HR05WA5025 (*Liquidambar styraciflua: *balsam); HD03WX5009 (*Liquidambar orientalis: *balsam); HR05WA5024 (*Liquidambar orientalis: *balsam).*
UNII — 63V91G4W93.

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

USP 36: (Storax). The balsam obtained from the trunk of *Liquidambar orientalis* (Levant storax) or *L. styraciflua* (American storax) (Hamamelidaceae). It is a semiliquid greyish to greyish-brown, sticky, opaque mass depositing on standing a heavy dark brown layer (Levant storax), or semisolid, sometimes a solid mass, softened by gently heating (American storax). It is transparent in thin layers, has a characteristic odour, and is more dense than water.

Insoluble in water; soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, in carbon disulfide, and in ether, some insoluble residue usually remaining.

Profile

Storax has actions similar to those of Peru balsam (p. 2587.1). Purified storax or prepared storax was formerly applied as an ointment in the treatment of parasitic skin diseases. Storax has a mild antiseptic action and is an ingredient of some preparations for upper respiratory-tract disorders and for application to skin and mucous membranes. Skin sensitisation has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Friar's Balsam; *NZ*: Frador†; *S.Afr.*: Turullington Tincture†; *UK*: Frador; Friars Balsam.

Pharmacopoeial Preparations
BP 2014: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
USP 36: Compound Benzoin Tincture.

Stramonium

Datura; Durmanový list (stramonium leaf); Dumaropių lapai (stramonium leaf); Estramonio; Hulluruohonlehti (stramonium leaf); Inferno; Jamestown Weed; Jimson Weed; Maszlaglevél (stramonium leaf); Stechapfel; Stramoine; Stramoine, feuille de (stramonium leaf); Stramonii folium (stramonium leaf); Stramoniumblad (stramonium leaf); Thornapple; Дурман Обыкновенный (*Datura stramonium*).
ATC Vet — QR038B03.
*ATC Herb — HA03YA5003 (*Datura stramonium: *leaf); HR03BB5001 (*Datum stramonium: *leaf).*
*UNII — G6W4F0V8Z3 (*Datura stramonium*); WQ9QD9P2XV (*Datura stramonium *leaf).*

NOTE. The terms Datura, Datura Herb, and Datura Leaf have been applied to preparations of various species of the genus Datura including *Datura metel*.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of stramonium:

Devil's weed; Loco weed.

Pharmacopoeias. *Eur.* (see p. vii) includes a monograph for Stramonium Leaf and Prepared Stramonium.

Ph. Eur. 8: (Stramonium Leaf; Stramonii Folium). It consists of the dried leaf or the dried leaf, flowering tops and occasionally fruit-bearing tops of *Datura stramonium* and its varieties. It contains not less than 0.25% of total alkaloids, calculated as hyoscyamine. The alkaloids consist mainly of hyoscyamine with varying proportions of hyoscine. It has an unpleasant odour. Protect from light and moisture.

The BP 2014 directs that when stramonium leaf or powdered stramonium leaf is prescribed, prepared stramonium shall be dispensed.

Ph. Eur. 8: (Stramonium, Prepared; Stramonii Pulvis Normatus). It is stramonium leaf powder adjusted to contain 0.23 to 0.27% of total alkaloids, calculated as hyoscyamine. Store in airtight containers. Protect from light.

Uses and Administration

Stramonium has the actions of atropine (p. 1312.1). It has been given with other drugs in oral and rectal dosage forms for respiratory-tract disorders. It has also been smoked in cigarettes or burnt in powders and the fumes inhaled but the irritation produced by the fumes may aggravate bronchitis.

Homoeopathy

Stramonium has been used in homoeopathic medicines under the following names: Datura stramonium; Stram.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p. 1312.1.

Abuse. Some reports of poisoning mostly associated with abuse of *Datura stramonium* or its preparations.

1. Gowdy JM. Stramonium intoxication: review of symptomatology in 212 cases. *JAMA* 1972; **221**: 585–7.
2. Shervette RE, *et al.* Jimson "Loco" weed abuse in adolescents. *Pediatrics* 1979; **63**: 520–3.
3. Anonymous. Jimson weed poisoning—Texas, New York, and California, 1994. *MMWR* 1995; **44**: 41–4.
4. Salen P, *et al.* Effect of physostigmine and gastric lavage in a Datura stramonium-induced anticholinergic poisoning epidemic. *Am J Emerg Med* 2003; **21**: 316–17.
5. Boumba VA, *et al.* Fatal poisoning from ingestion of Datura stramonium seeds. *Vet Hum Toxicol* 2004; **46**: 81–2.
6. Forrester MB. Jimsonweed (Datura stramonium) exposures in Texas, 1998-2004. *J Toxicol Environ Health A* 2006; **69**: 1757–62.
7. Marc B, *et al.* Intoxications aiguës à Datura stramonium aux urgences. *Presse Méd* 2007; **36**: 1399–1403.
8. Spina SP, Taddei A. Teenagers with Jimson weed (Datura stramonium) poisoning. *CJEM* 2007; **9**: 467–8.
9. Wiebe TH, *et al.* Angel's trumpet (Datura stramonium) poisoning and delirium in adolescents in Winnipeg, Manitoba: Summer 2006. *Paediatr Child Health* 2008; **13**: 193–6.
10. Suk SH, Kwak YT. Toxic encephalopathy after taking dried seeds of Datura stramonium in two elderly subjects. *Geriatr Gerontol Int* 2009; **9**: 326–8.
11. CDC. Jimsonweed poisoning associated with a homemade stew—Maryland, 2008. *MMWR* 2010; **59**: 102–4.

Effects on the eyes. Anisocoria (unequal dilatation of the pupils) developed after accidental entry of a piece of jimson weed *(Datura stramonium)* into a patient's eye while gardening.[1]

1. Savitt DL, *et al.* Anisocoria from Jimsonweed. *JAMA* 1986; **255**: 1439–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austria*: Mygale compositum†; *Canad.*: Barijodeel†; Breathe More; Homeogene 46; Kids Calm; Quietude; *Cz.*: Sedalia; *Fr.*: Abbe Chaupitre no 67†; Abbe Chaupitre no 6; Boripharm No 12†; Homeogene 46; Lobelia Complexe No 74†; Noctium; Oenanthe Crocata Complexe No 78; Quietude; Santaherba; Somnidoron; Tarentula Complexe No 71; Zincum Cyanidum Complexe No 101†; *Ger.*: A-Bomin; Asthmavowen-N†; *Neth.*: Quietude†; *Switz.*: Quietude; Sleepium; *USA*: Preferred Remedies Stress.

Streptodornase *(BAN, rINN)*

Estreptodornasa; Streptococcal Deoxyribonuclease; Streptodornaasi; Streptodornas; Streptodornasum; Стрептодорназа.

CAS — 37340-82-2.

UNII — DVBJ2R3544.

Profile

Streptodornase is an enzyme obtained from cultures of various strains of *Streptococcus haemolyticus*. It catalyses the depolymerisation of polymerised deoxyribonucleoproteins. It liquefies the viscous nucleoprotein of dead cells; it has no effect on living cells. It is used with streptokinase in the topical treatment of lesions, wounds, and other conditions that require the removal of clots or purulent matter; the combination may also be used to dissolve clots in the bladder or in urinary catheters.

It has also been given orally with streptokinase and sometimes with antibacterials, for its supposed benefit in reducing oedema and inflammation associated with trauma and infection.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Strontium Chloride

Estroncio, cloruro de; Stronsiyum Klorür; Strontii Chloridum; Strontiumklorid; Strontiumkloridi; Хлорид Стронция.

$SrCl_2.6H_2O$=266.6.

CAS — 10476-85-4 (anhydrous strontium chloride).

UNII — EKE8PS9J6Z (strontium chloride); O09USB7Z44 (strontium chloride hexahydrate).

Profile

Strontium chloride is used as a 10% toothpaste for the relief of dental hypersensitivity. Strontium acetate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sensodyne Original; *Austria*: Sensodyne med†; *Braz.*: Sensodyne Formula Original; *Canad.*: Sensodyne†; Zarosen†; *Chile*: Dentoxil†; *India*: Bentoform; Denex-S; *Turk.*: Sensodyne Mint; *UK*: Sensodyne Mint; Sensodyne Original; *USA*: Sensodyne-SC; *Venez.*: Sencia.

Multi-ingredient Preparations. *Arg.*: Esme Topico; Sensodyne Rapido Alivio; *Austral.*: Macleans Sensitive; *Ital.*: Pitiren; *Singapore*: 2Sensitive.

Homoeopathic Preparations. *Fr.*: Sepia Complexe No 20.

Strychnine ⊗

Estricnina; Strychnina.

Strychnidin-10-one.

$C_{21}H_{22}N_2O_2$=334.4

CAS — 57-24-9.

Description. Strychnine is an alkaloid obtained from the seeds of nux vomica (p. 2573.3) and other species of *Strychnos*.

Strychnine Hydrochloride ⊗

Estricnina, hidrocloruro de; Strych. Hydrochlor.; Strychninae Hydrochloridum.

$C_{21}H_{22}N_2O_2.HCl.2H_2O$=406.9

CAS — 1421-86-9 (anhydrous strychnine hydrochloride); 6101-04-8 (strychnine hydrochloride dihydrate).

Strychnine Nitrate ⊗

Azotato de Estricnina; Estricnina, nitrato de; Nitrato de Estricnina; Strychninae Nitras; Strychnini Nitras; Strychninum Nitricum; Strykniininitraatti; Strykninnitrat.

$C_{21}H_{22}N_2O_2.HNO_3$=397.4

CAS — 66-32-0.

UNII — O642E96711.

Pharmacopoeias. In *Chin.*

Strychnine Sulfate ⊗

Estricnina, sulfato de; Strychninae Sulphas; Strychnine Sulphate; Strychninum Sulfuricum; Sulfato de Estricnina.

$(C_{21}H_{22}N_2O_2)_2.H_2SO_4.5H_2O$=857.0

CAS — 60-41-3 (anhydrous strychnine sulfate); 60491-10-3 (strychnine sulfate pentahydrate).

UNII — FA486DV76S.

Pharmacopoeias. In *Fr.* and *Viet.*

Uses and Administration

Strychnine competes with glycine, which is an inhibitory neurotransmitter; it thus exerts a central stimulant effect by blocking an inhibitory activity.

Strychnine was formerly used as a bitter and analeptic but is now mainly used under strict control as a rodenticide. It has also been used as a mole poison, although this use is banned in some countries including the UK. Strychnine has been used in multi-ingredient preparations for the treatment of ophthalmic and urinary-tract disorders. It has also been tried in the treatment of nonketotic hyperglycinaemia.

Homoeopathy

Strychnine and its salts have been used in homoeopathic medicines under the following names:

- Strychnine: strychninum; strychninum purum; stry.
- Strychnine nitrate: strychninum nitricum; stry-n.
- Strychnine phosphate: strychninae phosphas; strychninum phosphoricum; strychnia phosphorica; stry-p.

Nonketotic hyperglycinaemia. Nonketotic hyperglycinaemia (also known as glycine encephalopathy) is an inborn defect in the enzyme system responsible for the metabolism of glycine. It is characterised by raised concentrations of glycine in plasma, CSF, and urine. Symptoms of glycine accumulation include respiratory distress, muscular hypotonia, seizures, vomiting, and extreme lethargy. Mental retardation and early infant death are common.

Sodium benzoate can reduce plasma-glycine concentrations to near normal[1] but is relatively ineffective in reducing CSF levels or in preventing mental retardation.[2] Strychnine, a glycine antagonist, has been of some benefit in counteracting its CNS effects.[3-5] However, even treatment with both drugs may be ineffective in severe cases[6] and may ultimately have little effect on the course of the disease.[7] Glycine is reported to stimulate *N*-methyl-D-aspartate (NMDA) receptors in the CNS and the combination of strychnine and ketamine (an NMDA receptor antagonist) was of some benefit in a newborn infant with severe nonketotic hyperglycinaemia.[8] Addition of low-dose dextromethorphan (an NMDA receptor antagonist) to treatment with sodium benzoate, arginine, carnitine, diazepam, and phenobarbital in an infant with nonketotic hyperglycinaemia[9] was associated with resolution of nystagmus and improvement in eye contact and interactive behaviour, without altering serum- or CSF-glycine concentrations. Dextromethorphan with sodium benzoate alone may also be helpful, although the combination is not uniformly effective.[10] Treatment with sodium benzoate and dextromethorphan was beneficial in a 6-month-old child with mild atypical nonketotic hyperglycinaemia,[11] although it was later shown that it was sodium benzoate that had the greatest effect on EEG and behavioural changes. A partial response to low-protein diet and sodium benzoate occurred in a patient with late-onset nonketotic hyperglycinaemia; there was a more dramatic response when imipramine was added to therapy.[12]

1. Van Hove JLK, *et al.* Benzoate treatment and the glycine index in nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2005; **28**: 651–63.
2. Krieger I, *et al.* Cerebrospinal fluid glycine in nonketotic hyperglycinemia: effect of treatment with sodium benzoate and a ventricular shunt. *Metabolism* 1977; **26**: 517–24.
3. Ch'ien LT, *et al.* Glycine encephalopathy. *N Engl J Med* 1978; **298**: 687.
4. Gitzelmann R, *et al.* Strychnine for the treatment of nonketotic hyperglycinaemia. *N Engl J Med* 1978; **298**: 1424.
5. Arneson D, *et al.* Strychnine therapy in nonketotic hyperglycinemia. *Pediatrics* 1979; **63**: 369–73.
6. Sankaran K, *et al.* Glycine encephalopathy in a neonate. *Clin Pediatr (Phila)* 1982; **21**: 636–7.
7. MacDermot KD, *et al.* Attempts at use of strychnine sulfate in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1980; **65**: 61–4.
8. Tegtmeyer-Metzdorf H, *et al.* Ketamine and strychnine treatment of an infant with nonketotic hyperglycinaemia. *Eur J Pediatr* 1995; **154**: 649–53.
9. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; **97**: 924–6.
10. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; **132**: 709–13.
11. Neuberger JM, *et al.* Effect of sodium benzoate in the treatment of atypical nonketotic hyperglycinaemia. *J Inherit Metab Dis* 2000; **23**: 22–6.
12. Wiltshire EJ, *et al.* Treatment of late-onset nonketotic hyperglycinaemia: effectiveness of imipramine and benzoate. *J Inherit Metab Dis* 2000; **23**: 15–21.

Adverse Effects

The symptoms of strychnine poisoning are mainly those arising from stimulation of the CNS. Early signs occurring within 15 to 30 minutes of ingestion include tremors, slight twitching, and stiffness of the face and limbs. Painful convulsions develop and may be triggered by minor sensory stimuli; since consciousness is not impaired patients may be extremely distressed. All forms of sensation are heightened. The body becomes arched backwards in hyperextension with the head retracted, arms and legs extended, fists clenched, and the feet turned inward. The jaw is rigidly clamped and contraction of the facial muscles produces a characteristic grinning expression known as 'risus sardonicus'. The convulsions may recur repeatedly and are interspersed with periods of relaxation. If not treated adequately, few patients survive more than 5 episodes of convulsions, death usually occurring due to respiratory and cardiac arrest. Fatalities in adults have occurred with doses as little as 16 mg.

Secondary effects arising from the severe spasms include lactic acidosis, rhabdomyolysis, renal failure, hyperthermia, hyperkalaemia, and dehydration.

Poisoning. References.

1. O'Callaghan WG, *et al.* Unusual strychnine poisoning and its treatment: report of eight cases. *BMJ* 1982; **285**: 478.
2. Blain PG, *et al.* Strychnine poisoning: abnormal eye movements. *J Toxicol Clin Toxicol* 1982; **19**: 215–17.
3. Boyd RE, *et al.* Strychnine poisoning: recovery from profound lactic acidosis, hyperthermia, and rhabdomyolysis. *Am J Med* 1983; **74**: 507–12.
4. Burn DJ, *et al.* Strychnine poisoning as an unusual cause of convulsions. *Postgrad Med J* 1989; **65**: 563–4.
5. Yamarick W, *et al.* Strychnine poisoning in an adolescent. *J Toxicol Clin Toxicol* 1992; **30**: 141–8.
6. Heiser JM, *et al.* Massive strychnine intoxication: serial blood levels in a fatal case. *J Toxicol Clin Toxicol* 1992; **30**: 269–83.
7. Nishiyama T, Nagase M. Strychnine poisoning: natural course of a nonfatal case. *Am J Emerg Med* 1995; **13**: 172–3.
8. Katz J, *et al.* Strychnine poisoning from a Cambodian traditional remedy. *Am J Emerg Med* 1996; **14**: 475–7.
9. Hernandez AF, *et al.* Acute chemical pancreatitis associated with nonfatal strychnine poisoning. *J Toxicol Clin Toxicol* 1998; **36**: 67–71.
10. Greene R, Meatherall R. Dermal exposure to strychnine. *J Anal Toxicol* 2001; **25**: 344–7.
11. Wood D, *et al.* Case report: survival after deliberate strychnine self-poisoning, with toxicokinetic data. *Crit Care* 2002; **6**: 456–9.
12. Scheffold N, *et al.* Strychninvergiftung. *Dtsch Med Wochenschr* 2004; **129**: 2236–8.
13. Shadnia S, *et al.* A case of acute strychnine poisoning. *Vet Hum Toxicol* 2004; **46**: 76–9.

Treatment of Adverse Effects

The main aim of therapy in strychnine poisoning is the prompt prevention or control of convulsions and asphyxia. Activated charcoal should be given if the patient presents within 1 hour of ingestion. Convulsions should be

controlled or prevented by diazepam or lorazepam. Intubation and assisted respiration may be required. Should benzodiazepines fail then phenytoin or phenobarbital may be tried. All unnecessary external stimuli should be avoided and if possible the patient should be kept at rest in a quiet darkened room. Patients should be monitored for any secondary effects such as metabolic acidosis so that appropriate symptomatic treatment can be given.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Vigofortal†; *Pol.*: Cardiamid-Coffein†; *Thai.*: Hemo-Cyto-Serum†.

Homoeopathic Preparations. *Fr.*: Conium Complexe No 36†; Diabene; Sativol†; *Neth.*: Sativol†.

Suanzaorentang

Ziziphus Soup.

Profile

Suanzaorentang is a traditional Chinese remedy for anxiety and insomnia. It contains five herbs: suanzaoren (*Zizyphus spinosus*, Rhamnaceae), fuling (*Poria cocos*, Polyporaceae), gancao (*Glycyrrhiza uralensis*, Leguminosae), zhimu (*Anemarrhena asphodeloides*, Liliaceae), and chuanxiong (*Ligusticum chuanxiong*, Umbelliferae).

Subtilisin A ⊗

EC 3.4.21.62; Subtilisin Carlsberg; Subtilopeptidase A; Субтилизин А.
CAS — 9014-01-1 (subtilisin).

Profile

Subtilisins are a class of serine proteases isolated initially from *Bacillus subtilis* but which are also excreted by other *Bacillus* species. They are widely used in the manufacture of enzymatic detergents. Hypersensitivity reactions have been reported.

Subtilisin A, which is obtained from *Bacillus licheniformis*, is used as an enzymatic cleanser for contact lenses.

References.
1. Lemiere C, *et al.* Isolated late asthmatic reaction after exposure to a high-molecular-weight occupational agent, subtilisin. *Chest* 1996; 110: 823–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Naclens; Ultrazyme; *Austral.*: Complete Protein Remover†; Ultrazyme; *Canad.*: Ultrazyme†; Unizyme†; *NZ*: Ultrazyme; *Turk.*: Unizyme; *USA*: Renu Enzymatic Cleaner†; Soft Mate Enzyme Plus Cleaner; Ultrazyme.

Succinic Dinitrile

Butanedinitrile; Cyanure d'éthylène; Ethylene Cyanide; Ethylene Dicyanide; Succinic Acid Dinitrile; Succinonitrile; Sukkinonitriili.
1,2-Dicyanoethane.
$C_4H_4N_2$=80.09
CAS — 110-61-2.
UNII — 1R479O92DO.

Profile

Succinic dinitrile is a cyanide compound and shares their toxicity (see Adverse Effects under Hydrocyanic Acid, p. 2156.2). It has industrial uses and has also been used in preparations for nervous disorders and in tonics.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Enervit; *Venez.*: Dinitrile-Vit; Dinitro-B.

Sulfan Blue *(BAN)*

Azul sulfán; Błękit sulfanowy; Blue VRS; Isosulfan Blue (USAN); P-1888; P-4125; Sulphan Blue.
Sodium α-(4-diethylaminophenyl)-α-(4-diethyliminiocyclohexa-2,5-dienylidene)toluene-2,5-disulfonate.
$C_{27}H_{31}N_2NaO_6S_2$=566.7
CAS — 68238-36-8 (2,5-disulfonate isomer); 129-17-9 (2,4-disulfonate isomer).
UNII — FH1929KTT (sulfan blue); 39N9K8S2A4 (isosulfan blue).

NOTE. Sulfan blue was formerly described in *BPC 1954* as the 2,4-disulfonate isomer and the following synonyms have been applied to this 2,4-isomer: Acid Blue 1; Alphazurine 2G; Colour Index No. 42045; Patent Blue V; Sulphanum Caeruleum. The name Patent Blue V, however, is mainly used for CI No. 42051 (p. 2584.2).

Profile

Sulfan blue 1% solution is injected subcutaneously to outline the lymph vessels as an adjunct to lymphography. It was formerly given intravenously as a visual test of the circulation in normal and damaged tissue.

Sulfan blue is reported to be incompatible with local anaesthetics, such as lidocaine.

Urine may be coloured blue for 24 hours, and transient or long-term blue coloration of the skin can occur after subcutaneous use. Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, pruritus, and asthma attacks have been reported. Cross-sensitivity with patent blue V has been reported (see p. 2584.3). Sulfan blue has also been reported to interfere with blood tests for protein and iron. It may also cause falsely low measurements of oxygen saturation in peripheral blood by pulse oximetry and falsely elevated readings of methaemoglobin by arterial blood gas analyser.

References.
1. Kaufman G, *et al.* A cautionary tale: anaphylaxis to isosulfan blue dye after 12 years and 3339 cases of lymphatic mapping. *Am Surg* 2008; 74: 152–5.
2. Bézu C, *et al.* Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg Oncol* 2011; 20: e55–9.
3. Gur L *et al.* Sudden false oxygen desaturation and facitious methemoglobinemia after subcutaneous injection of isosulfan blue (Lymphazurin). *Am Surg* 2011; 77: 383–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Lymphazurin†; *Gr.*: Lymphazurin; *USA*: Lymphazurin.

Sulfobromophthalein Sodium *(BANM)*

Bromsulfophthalein Sodium; Bromsulphthalein Sodium; BSP; SBP; Sodium Sulfobromophthalein; Sulfobromoftaleína sódica; Sulphobromophthalein Sodium; Сульфобромфталеин Натрия.
Disodium 4,5,6,7-tetrabromophenolphthalein-3′,3″-disulphonate; Disodium 5,5′-(4,5,6,7-tetrabromophthalidylidene) bis(2-hydroxybenzenesulphonate).
$C_{20}H_8Br_4Na_2O_{10}S_2$=838.0
CAS — 297-83-6 (sulfobromophthalein); 71-67-0 (sulfobromophthalein sodium).
ATC — V04CE02.
ATC Vet — QV04CE02.
UNII — 62E5JU30OV.

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

Profile

In patients with normal hepatic function sulfobromophthalein sodium is rapidly extracted, conjugated, and excreted in bile. It was formerly used intravenously as a diagnostic agent for testing the functional capacity of the liver but may cause severe hypersensitivity reactions.

Sulfur Iodide

Iodosulfane; Sulphur Iodide.
CAS — 1312-15-8.
UNII — L6L8KA2AA0.

Profile

Sulfur iodide is obtained by fusing sulfur (p. 1721.1) with iodine (p. 2336.3).

Homoeopathy

Sulfur iodide has been used in homoeopathic medicines under the following names: Sulfur iodatum; Iodure de soufre.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Acne; ClearAct†; Hylands Formula CA; Phyto-Cal; *Fr.*: Boripharm No 22†; Osteocynesine; *Ger.*: Pascoleucyn; Steiroderm; *Neth.*: Kind 0-6 Caltrivat; Osteocynesine†; *Port.*: Osteocynesine; *Switz.*: Exsepta; Regenaplex Nr. 31b; *Ukr.*: Immunokind (Иммунокинд).

Sulfuric Acid

Acid. Sulph.; Acid. Sulph. Dil.; Acide sulfurique; Acidum sulfuricum; E513; Kénsav; Kwas siarkowy; Kyselina sírová; Oil of Vitriol; Rikkihappo; Schwefelsäure; Sulfato rūgštis; Sulfúrico, ácido; Sulphuric Acid; Svavelsyra; Verdünnte Schwefelsäure (dilute sulfuric acid).
H_2SO_4=98.07
CAS — 7664-93-9.
UNII — O40UQP6WCF.

NOTE. Concentrated oil of vitriol of commerce, 'COV' contains about 95 to 98% w/w, and brown oil of vitriol 'BOV', contains 75 to 85% w/w of H_2SO_4.

Nordhausen or fuming sulfuric acid, 'Oleum', is sulfuric acid containing SO_3.

Battery or accumulator acid is sulfuric acid diluted with distilled water to a specific gravity of 1.2 to 1.26.

Pharmacopoeias. *Br.* and *Eur.* (see p. vii) include various concentrations. Also in *USNF*.

BP 2014: (Dilute Sulfuric Acid). It contains 9.5 to 10.5% w/w of H_2SO_4 and is prepared by adding 104 g of sulfuric acid to 896 g of water, with constant stirring and cooling.

Ph. Eur. 8: (Sulfuric Acid). It contains 95.0 to 100.5% w/w of H_2SO_4. A colourless, very hygroscopic, oily liquid. Miscible with water and with alcohol producing intense heat. Store in airtight containers.

USNF 31: (Sulfuric Acid). It contains 95.0 to 98.0% w/w of H_2SO_4. A clear, colourless, oily liquid. Is very caustic and corrosive. Miscible with water and with alcohol with the generation of much heat. Store in airtight containers.

Dilution. When sulfuric acid is mixed with other liquids, it should always be added slowly, with constant stirring, to the diluent.

Uses and Administration

Sulfuric acid has various industrial uses. Dilute sulfuric acid has been used as an astringent in diarrhoea and it has occasionally been prescribed in mixtures with vegetable bitters to stimulate appetite.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Oralmedic; *UK*: Oralmedic; *USA*: Debacterol.

Homoeopathic Preparations. *Canad.*: Adrisin†; Bioactiv H†; *Chile*: Bioactiv H; *Fr.*: Aftosium; Gentiana Complexe No 33†; Homeoaftyl; *Ger.*: Lowe-Komplex Nr 6; Panalgan; Secale-Gastreu; *Neth.*: Opsonat; *Rus.*: Nux Vom-Plus (Нукс Вом-Плюс); *Switz.*: Regenaplex Nr. 51c.

Pharmacopoeial Preparations
USP 36: Ferric Subsulfate Solution.

Sumatra Benzoin

Benjoim; Benjoin; Benjoin de sumatra; Benjuí; bálsamo de; Benzoë; Benzoe, Sumatra-; Benzoe sumatranus; Benzoin; Benzoina; Gum Benjamin; Gum Benzoin; Styrax tonkinensis et Styrax benzoin; Суматранский бензоин.
CAS — 9000-05-9.
ATC Herb — HR05WA5053 (Styrax paraleloneurum: resin); HR05WA5052 (Styrax benzoin: resin); HD02WX5005 (Styrax benzoin: resin); HD02WX5006 (Styrax paraleloneurum: resin).

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

US allows both Siam benzoin and Sumatra benzoin under the title Benzoin.

Ph. Eur. 8: (Sumatra Benzoin). A resin obtained by incising the trunk of *Styrax benzoin*. It contains 25 to 50% of total acids, calculated as benzoic acid (dried drug).

Creamy white, rounded to ovoid tears, which may be embedded in a dull, greyish-brown or reddish-brown matrix. It is hard and brittle and the fractured surface is dull and uneven.

USP 36: (Benzoin). A balsamic resin from *Styrax paralleloneurus* or *S. benzoin* (Styracaceae). It yields not less than 75% of alcohol-soluble extractive. It occurs as blocks or lumps of variable size made up of tears, compacted together, with a reddish-brown, reddish-grey, or greyish-brown resinous mass. The tears are externally yellowish or rusty brown, milky white on fresh fracture, hard and brittle at ordinary temperatures but softened by heat. It has an aromatic and balsamic odour. When heated it does not emit a pinaceous odour. When digested with boiling water, the odour suggests cinnamates or storax.

Profile

Sumatra benzoin is an ingredient of inhalations that are used in the treatment of catarrh of the upper respiratory

tract. Sumatra benzoin is also used in topical preparations for its antiseptic and protective properties. Skin sensitisation has been reported.

Preparations of Sumatra benzoin are used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Benzoinspray.

Multi-ingredient Preparations. *Belg.*: Borostyrol; *Braz.*: Inhalante Yatropan; *Canad.*: Cold Sore Lotion; Skin-B-Dip; *Fr.*: Balsofumine; Dolirhume; *Israel*: Kank-A; *Ital.*: Citrosil Nubesan; Fomentil; *NZ*: Cold Sore†; *Port.*: Vaporil; *S.Afr.*: Turulington Tincture†; *Switz.*: Baume Zeller; Pommade au Baume; *Turk.*: Buguseptil; Rinolar; *UK*: Allens Dry Tickly Cough; Frador; Friars Balsam; Kilkof; Potters Strong Bronchial Catarrh Pastilles; Potters Sugar Free Cough Pastilles; Snowfire; Throaties Pastilles; *USA*: Pfeiffer's Cold Sore; *Venez.*: Aftil.

Pharmacopoeial Preparations
BP 2014: Benzoin Inhalation; Compound Benzoin Tincture;
BPC 1954: Compound Iodoform Paint;
Ph. Bur.: Benzoin Tincture, Sumatra;
USP 36: Compound Benzoin Tincture; Podophyllum Resin Topical Solution.

Summer Savory

Bohnenkraut; Sarriette; Savory; Чабёр Садовый.
UNII — RU34I39IYL.

Profile

Summer savory (*Satureja hortensis*, Lamiaceae) is included in herbal preparations and is used as a culinary herb.

It is the source of savory oil which is included in herbal preparations, mainly for the relief of cold symptoms. It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Gartech†; *Fr.*: Resistim; *Rus.*: Maraslavin (Мараславин); *Spain*: Tonimax; *Switz.*: Demonatur Capsules contre les refroidissements; Echinarom; Spagyrom.

Surgibone *(USAN)*

Profile

Surgibone is sterile, specially processed mature bovine bone, that has been used for grafting procedures in orthopaedic and reconstructive surgery.

Sweet Chestnut

Aito Kastanja; Äkta Kastanj; Castanheiro-comum; Castaño; Castaño Común; Châtaignier; Châtaignier Commun; Chestnut; Edelkastanie; Esskastanie; European Chestnut; Jalokastanja; Kastanie; Marone; Spanish Chestnut.
ATC Herb — HR05DB5004 (Castanea sativa: *leaf*); *HD03WA5002* (Castanea sativa: *leaf*).
UNII — DK55N3C1AK (Castanea sativa); *PK19Q4Q3Y4* (Castanea sativa *bark*); *YHZ719F7M3* (Castanea sativa *flower*); *IV3S2HH53G* (Castanea sativa *leaf*); *2MT5XMR2YW* (Castanea sativa *nut*); *F71O639GCL* (Castanea sativa *shell*).

NOTE. The name Spanish Chestnut has been applied both to Sweet Chestnut and to Aesculus (p. 2431.2).

Profile

The leaves of sweet chestnut, *Castanea sativa* (*C. vesca*; *C. vulgaris*) (Fagaceae) have traditionally been included in herbal medicines for cough and other respiratory disorders. They have also been used for circulatory disorders.

The fruits are used as a foodstuff, usually roasted.

The American chestnut, *C. dentata* has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: LF 100.

Multi-ingredient Preparations. *Austria*: Brust- und Hustentee St Severin; Tussamag; *Fr.*: Calmiflorine†; *Ger.*: Equisil N†; *Ital.*: Broncosed; Tussamag; *Switz.*: Siropectan; *Venez.*: T-Samag.

Tafamidis *(USAN, rINN)*

FX-1006; Tafamidisum; Тафамидис.
2-(3,5-Dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid.
$C_{14}H_7Cl_2NO_3$=308.1.
CAS — 594839-88-0.
UNII — 8FG9H9D31J.

Tafamidis Meglumine *(USAN, rINN)*

FX-1006A; Meglumini Tafamidisum; Tafamidis meglumina; Tafamidis Méglumine; Тафамидис Меглюмин.
D-*gluco*-2,3,4,5,6-Pentahydroxy-*N*-methylhexan-1-aminium 2-(3,5-dichlorophenyl)benzoxazole-6-carboxylate.
$C_{14}H_7Cl_2NO_3.C_7H_{17}NO_5$=503.3.
CAS — 951395-08-7.
UNII — ZU7CF08A1A.

Profile

Tafamidis stabilises transthyretin thereby inhibiting amyloid formation in the hereditary disease familial ATTR amyloidosis (transthyretin amyloidosis; familial amyloid polyneuropathy; see Amyloidosis, p. 819.3) with the potential to delay peripheral neurological impairment. It is used for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy. Tafamidis is given as the meglumine, but doses are expressed in terms of the base; tafamidis meglumine 32.7 mg is equivalent to about 20 mg of tafamidis. The usual oral dose is equivalent to 20 mg of tafamidis once daily. Commonly reported adverse effects include gastrointestinal complaints and urinary-tract or vaginal infections.

References.
1. Said G. *et al.* Tafamidis. *Nat Rev Drug Discov* 2012; 11: 185–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Vyndaqel; *Denm.*: Vyndaqel; *Fr.*: Vyndaqel; *Irl.*: Vyndaqel; *Neth.*: Vyndaqel; *Swed.*: Vyndaqel; *UK*: Vyndaqel.

Taltirelin *(rINN)*

TA-0910; Taltirelina; Taltiréline; Taltirelinum; Тальтирелин.
(-)-*N*-[[(*S*)-Hexahydro-1-methyl-2,6-dioxo-4-pyrimidinyl]carbonyl]-L-histidyl-L-prolinamide.
$C_{17}H_{23}N_7O_5$=405.4.
CAS — 103300-74-9.
UNII — DOZ 62MV6A5.

Profile

Taltirelin is an analogue of protirelin (p. 2344.2) and is claimed to have beneficial effects on CNS function. It is used in the treatment of spinocerebellar degeneration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Ceredist.

Tannic Acid

Acide tannique; Acidum Tannicum; Gallotannic Acid; Garvsyra; Gerbstoff; Kwas taninowy; Tánico, ácido; Tanin; Tanina; Taninas; Tann. Acid; Tanniini (Parkkihappo); Tannin; Tanninum; Дубильная Кислота.
CAS — 1401-55-4.
UNII — 28F9E0DJY6 (*tannic acid*); *P4J83159H6* (*tannic acid from* Caealpinia spinosa *seed*); *2711I21VE5* (*tannic acid from* Quercus Infectoria *nutgall*); *5PG9M8BASQ* (*tannic acid from* Quercus*spp. nutgall*); *54OM1T1DZQ* (*tannic acid from* Rhus*spp. leaf*); *41F04WC310* (*tannic acid from* Rhus*spp. nutgall*).

NOTE. In pharmaceutical literature, the name digallic acid is frequently confused with tannic acid.

Commercial grades of tannic acid may contain gallic acid and being less soluble are not suitable for medicinal use.

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

Ph. Eur. 8: (Tannic Acid). A mixture of esters of glucose with gallic acid and 3-galloylgallic acid. A yellowish-white or slightly brown amorphous light powder or shiny plates. Very soluble in water; freely soluble in alcohol, in acetone, and in glycerol (85%); practically insoluble in dichloromethane. Protect from light.

USP 36: (Tannic Acid). A tannin usually obtained from nutgalls (see Gall, p. 2508.3), the excrescences produced on the young twigs of *Quercus infectoria* and allied species of *Quercus*, from the seed pods of tara (*Caesalpinia spinosa*), or from the nutgalls or leaves of sumac (any of genus *Rhus*). Amorphous powder, glistening scales, or spongy masses, varying in colour from yellowish-white to light brown. Is odourless or has a faint, characteristic odour. Very soluble in water, in alcohol, and in acetone; freely soluble in diluted alcohol; slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ether, in petroleum spirit, and in benzene; soluble 1 in about 1 of warm glycerol. Store in airtight containers. Protect from light.

Profile

Tannic acid has been used as an astringent for the mucous membranes of the mouth and throat, and in suppositories for the treatment of haemorrhoids. It is an ingredient in several dermatological preparations.

Former uses of tannic acid include application to burns, addition to barium sulfate enemas to improve the quality of radiological pictures of the colon, and as an ingredient of 'Universal Antidote'. However, tannic acid has been associated with liver toxicity, sometimes fatal.

Tattoo removal. Although tannic acid may be used by plastic surgeons and dermatologists to produce a controlled partial-thickness burn in tattoo removal[1] it has been pointed out that in unskilled or amateur hands this procedure has resulted in full thickness burns requiring skin grafting to obtain satisfactory healing.[2]

1. Mercer NSG, Davies DM. Tattoos. *BMJ* 1991; 303: 380.
2. Scott M, Ridings P. Tattoos. *BMJ* 1991; 303: 720.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Tanagel Polvo; *Switz.*: Tanno-Hermal.

Multi-ingredient Preparations. *Austral.*: SM-33; *Austria*: Haemanal; *Belg.*: Hemorhinol†; *Braz.*: Anapyon; Lacto Vagin; *Canad.*: Tanac; *Chile*: Paralymphine; *Fr.*: HEC; *Ger.*: Eulatin NH; Eulatin NH; *Gr.*: Oulogram; *India*: Arofil; Clenora; Clenorush; Cureg; Dentakind; Dordent; Icée; Klinit; Me-Fresh Gum Paint; O2-Fresh-GP; Ora-G; Orex; *Irl.*: Phytex†; *Israel*: Rectozorin; *Ital.*: Blefarolin; Neo Emocicatrol; *Philipp.*: Zilactin; *Pol.*: Acifungin; Salumin†; *Rus.*: Contraceptin T (Контрацептин Т); Neo-Anusol (Нео-анузол); *Spain*: Antihemorroidal; Depurativo Richelet†; Dextricea†; Tanagel; *Switz.*: Eau Precieuse; HEC†; Tanno-Hermal; *Turk.*: Derisept0l; *UK*: Colsor; Phytex; TCP; *USA*: Dermasept Antifungal; Orasept†; Outgro; Tanac Dual Core; Tanac.

Tansy

Atanasia; Barbotine; Hierba lombriguera; Rainfarn; Tanaceto; Tanaisie; Пижма.
UNII — D52957JQ8M.

NOTE. Distinguish from tansy ragwort which is *Senecio jacobaea* (see Senecio p. 2612.3), a different plant and a common cause of livestock poisoning.

Profile

Tansy, the flowering tops of *Tanacetum vulgare* (*Chrysanthemum vulgare*) (Compositae), has been used as an anthelmintic and to stimulate menstruation. The oil is highly toxic and use of tansy is generally not recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Calmo†; *Pol.*: Artemisol.

Taraxacum

Dandelion Root; Diente de León; Korzeń mniszka (root); Löwenzahnwurzel; Pissenlit; Taraxaci Herba; Taraxaci Radix (root); Taraxacum officinalis; Taraxacum Root; Одуванчик Лекарственный (*Taraxacum officinale*); Ziele mniszka.
ATC Herb — HA05AW5017 (Taraxacum officinale sensu auct. *root*); *HA05AW5016* (Taraxacum officinale sensu auct. *leaf*); *HA06AX5011* (Taraxacum officinale sensu auct. *root*); *HA09WA5025* (Taraxacum officinale sensu auct. *root*); *HA06AX5010* (Taraxacum officinale sensu auct. *leaf*).
UNII — 39981FM375 (Taraxacum officinale); *DQS85W46HV* (Taraxacum officinale *flowering top*); *0022LFJ74Y* (Taraxacum officinale *leaf*); *9DE5YCO0RU* (Taraxacum officinale *root*).

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

Chin. specifies Taraxacum Herb from other species of *Taraxacum*.

Ph. Bur. 8: (Dandelion Herb with Root; Taraxaci Officinalis Herba cum Radice). A mixture of the whole or fragmented, dried aerial and underground parts of *Taraxacum officinale*. It has a bitter taste.

Ph. Eur. 8: (Dandelion Root); Taraxaci Officinalis Radix. A mixture of the whole or cut, dried underground parts of *Taraxacum officinale*. It has a bitter taste.

Profile

Taraxacum is the fresh or dried root of the common dandelion, *Taraxacum officinale* (Compositae). It has been used as a bitter, as a diuretic, and as a mild laxative.

Homoeopathy

Taraxacum has been used in homoeopathic medicines under the following names: Taraxacum officinale; Taraxacum officinale, radix; Taraxacum, rad; Tarax.

References.

1. Houghton P. Bearberry. dandelion and celery. *Pharm J* 1995; **255:** 272–3.
2. Sweeney B, *et al.* Evidence-based systematic review of dandelion (*Taraxacum officinale*) by Natural Standard Research Collaboration. *J Herb Pharmacother* 2005; **5:** 79–93.
3. Goksu E, *et al.* First report of hypoglycemia secondary to dandelion (Taraxacum officinale) ingestion. *Am J Emerg Med* 2010; **28:** 111.e1–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Paverysat L; *Pol.*: Talion.

Multi-ingredient Preparations. *Arg.*: Desgras Complex; Quelodin F; *Austral.*: Berberis Complex†; Colax†; Colax; Cranbiotic Super†; Detox Program; DiGest; Digestive Bitters; Extralife Fluid-Care†; Extralife Liva-Care†; Feminine Herbal Complex; GR² Control Thermogenic Enhancer; Liver Detox; Liver Tonic Complex; Livton Complex; St Mary's Thistle Plus†; Toxicol; Vegie Digestaid; *Austria*: Gallen- und Lebertee St Severin; Gallesyn neu; Gallesyn neu; Magentee St Severin; Montana; Urelium Neu; *Canad.*: Anti Dyspepsia Digestive Aid†; Biliherb; Cellutex; Depuratif des Trappistes; Diuretic Formula; Duo-Bil; Gallexier†; Hepatol; Herbanat†; Intestinal Bulking Agent II†; Metab Herbs No 1†; Metab Herbs†; Milk Thistle Extract Formula; Phyto-Marinex; Special Formula Bulking Agent†; Traditional Herbal Laxative†; *Cz.*: Diabetan; Diabeticka Cajova Smes-Megadiabetin†; Original Schwedenbitter; The Salvat; *Fr.*: Aromadigest†; Biofirm; Drainuryl; Expuryl; Gastrotisane†; Hepatoflorine†; Hydracur; Romarene†; *Ger.*: Alasenn; Amara-Tropfen; Carmol Magen-Galle-Darm†; Gallemolan forte†; Gallexier; Gallexier; Hevert Stoffwechsel-Tee N†; Imupret; *Hong Kong*: Hepatofalk†; *Hung.*: Diabess; Gallexier; Majvedo es Detoxikalo; Montana; Vensaxa; Zeatax; *Indon.*: DFM; Proliva; *Ital.*: Cinarepa; Idren; Linfoguard†; *Mon.*: Romarinex Chrome; *Philipp.*: Completia†; Hepamin; *Pol.*: Artecholin†; Artecholwex†; Cholavisol; Cholesol; Cholitol; Diabetosol; Dyspepsin; Gastrobonisol; Nefrobonisol; Nefrol; Tabletki Przeciw Niestrawnosci; *Rus.*: Sodecor (Содекор); Tonsilgon N (Тонзилгон Н); *S.Afr.*: Amara†; *Spain*: Diurette†; *Swed.*: Cynaramin; *Switz.*: Boldocynara; Gastrosan; Gouttes Amara; Kernosan 24; Kernosan 26; Strath Gouttes pour les reins et la vessie; Tisane hepatique et biliaire; *UK*: Adios; Aqualette; Aquella; Backache; Boldex; Cassilax; Digestisan; HealthAid Boldo-Plus; Herbulax; HRI Water Balance; Lowater; Milk Thistle Complex; Natravene; Natural Herb Tablets; Out-of-Sorts; Pure Plan; Rheumatic Pain; Senokot Dual Relief; Stomach Mixture; Uvacin; Weight Loss Aid; Wind & Dyspepsia Relief; *Ukr.*: Detoxil (Детоксил); Imupret (Имупрет); Mammoleptin (Мамолептин); Tonsilgon N (Тонзилгон)†; *USA*: Clinical Nutrients Prenatal Formula; *Venez.*: Celyth's; Flocadep; Rheu-Tarx 1.

Homoeopathic Preparations. *Austria*: Galstena; Lymphdiaral; Taraxacum Med Complex; *Canad.*: Amaratopfen†; Carduus Plex†; Chelidonium Plex†; Common Mallow Combination†; Cynara Complex†; Dandelion Combination†; Formula FV 213; Hecocur†; Hepar Compositum; Lympatox; Pollen Plus; Yellow Dock Combination†; *Chile*: Cynara Compuesta; Digherbal; *Fr.*: Chelidonium Compose; Diabene; Diacure; Digeodren; Hepatopan†; Homeogene 22†; Yucca Complexe No 110; *Ger.*: Bomagall; Chelidonium comp; Chol-Do; Chole-cyl L Ho-Len-Complex; Cholo 2-injektopas; Derivatio H; Derivatio; Galloselect; HanoHepan; Hepa-Loges N; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Heparanox H; Hepatorell H Leber-Spezifikum; Homviohepan; Leber-Galletropfen; Lymphdiaral; Metaharonga; Pankreaticum; Pankreaticum; Taraxan; *Hung.*: Pro-Aller; *Neth.*: Apo-Hepat; Apo-Rheum†; Dolilite; Hepalite; Hepeel H; Lymphdiaral; Reudol; *Rus.*: Berberis-Plus (Берберис-Плюс); Galstena (Галстена); *Switz.*: Regenaplex Nr. 79; Regenaplex Nr. 80aN; *Ukr.*: Galstena (Галстена); *USA*: Preferred Remedies Detoxin.

Tartaric Acid

Acide tartrique; Acidum Tartaricum; Borkósav; E334; E353 (metatartaric acid); Kwas winowy; Kyselina vinná; Tart Acid; Tartárico, ácido; Tartarik Asit; Tarttique (Acide); Viinihappo; Vinsyra; Vyno rūgštis; Weinsäure; Виннокаменная Кислота; Винная Кислота.

(+)-L-Tartaric acid; (2*R*,3*R*)-2,3-Dihydroxybutane-1,4-dioic acid.

$C_4H_6O_6$=150.1

CAS — 87-69-4; 526-83-0.

UNII — W4888I119H.

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

Ph. Eur. 8: (Tartaric Acid). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol.

USNF 31: (Tartaric Acid). Colourless or translucent crystals or a white, fine to granular, crystalline powder. Is odourless. Soluble 1 in 0.8 of water, 1 in 0.5 of boiling water, 1 in 3 of alcohol, 1 in 250 of ether, and 1 in 1.7 of methyl alcohol.

Uses and Administration

Tartaric acid is used in the preparation of effervescent powders, granules, and tablets, as an ingredient of cooling drinks, and as a saline purgative. If not neutralised, it must be taken well diluted. Tartaric acid or metatartaric acid are used in wine-making as de-acidifying agents to assist in the removal of excess malic acid by forming an insoluble double salt with calcium carbonate.

Adverse Effects

Strong solutions of tartaric acid are mildly irritant and if ingested undiluted may cause violent vomiting and diarrhoea, abdominal pain, and thirst. Cardiovascular collapse or acute renal failure may follow.

Pharmacokinetics

Tartaric acid is absorbed from the gastrointestinal tract but up to 80% of an ingested dose is probably destroyed by micro-organisms in the lumen of the intestine before absorption occurs. Absorbed tartaric acid is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Yasta; *Austral.*: Citralite†; Citravescent; Dexsal†; Salvital; Ural; *Austria*: Duplotrast Weinsaure; Helo-acid; *Canad.*: Baros†; Lithines du Dr Gustin†; *Chile*: Prunalia†; Frutasal Knop; Uroknop; *Denm.*: Samarin; *Fr.*: Dermacide; Zeniac LP Fort; *Ger.*: Eubiolac; Retterspitz Ausserlich; Retterspitz Innerlich; *Gr.*: Coup-Lax Compose; Dermacide; Eno; *Hong Kong*: Baros†; *Hung.*: Samarin; *India*: Citro-Soda; Urisoda; *Ital.*: Antimicotica Solforata†; Geffer; Magnesia Effervescente Sella; *Malaysia*: Ezee; U-Lite; Ural; Urisoda; *NZ*: Ural; *Philipp.*: Ural; *Port.*: Safrux†; *S.Afr.*: Adco-Sodasol; Alkafizz; Citro-Soda; Quatro-Soda; Uri-Alk; *Singapore*: Citravescent; Uricalm; *Spain*: Citinoides†; Hectonona; Salcedol; Sales Fruta Mag Viviar†; Salmagne; *Swed.*: Samarin; *Switz.*: Siesta-1; *Thai.*: TAP†; *Turk.*: Enhos; Purgyl; Radyobarit-Double Contrast; *UK*: Jaaps Health Salt; *USA*: Baros†.

Taurine *(BAN, rINN)*

Taurina; Taurinum; Таурин.

2-Aminoethanesulphonic acid.

$C_2H_7NO_3S$=125.1

CAS — 107-35-7.

UNII — 1EQV5MLY3D.

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

USP 36: (Taurine). White crystals or crystalline powder. Soluble in water.

Profile

Taurine is an amino acid known to be involved in bile acid conjugation as well as other physiological functions. It has been included in preparations for parenteral nutrition of low-birth-weight infants and in infant formulas but its role as an essential nutrient has not been established.

Taurine is included in some preparations for cardiovascular and metabolic disorders.

References.

1. Redmond HP, *et al.* Immunonutrition: the role of taurine. *Nutrition* 1998; **14:** 599–604.
2. Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: experimental and clinical studies. *Amino Acids* 2002; **23:** 381–93.
3. Bidri M, Choay P. La taurine: un aminoacide particulier aux fonctions multiples. *Ann Pharm Fr* 2003; **61:** 385–91.
4. Kingston R, *et al.* The therapeutic role of taurine in ischaemia-reperfusion injury. *Curr Pharm Des* 2004; **10:** 2401–10.
5. Franconi F, *et al.* Taurine supplementation and diabetes mellitus. *Curr Opin Clin Nutr Metab Care* 2006; **9:** 32–6.
6. Verner AM, *et al.* Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Tairuining (泰瑞宁); Xiao Le Dun (小乐敦); *Ital.*: O-Due; *Philipp.*: Taurex; *Rus.*: Dibicor (Дибикор); Taufon (Тауфон).

Multi-ingredient Preparations. *Arg.*: Synapsys; *Austral.*: Liver Detox; Liver Tonic Complex; PM Syrin; *Belg.*: Ostrin Q10; *China*: Run Jie (润洁); Zhongxin (中鑫); *Fr.*: D-Stress; Formag; Phytozac; *India*: Diapill; Nefrosave; *Indon.*: Asten; Biofos†; Fitkom; Growee; Hemaviton Energy Drink; Hemaviton Jreng; Lanavision Plus; nutrivision; Proview; Regresor; Sangobion ActiFe; Vidoran Smart Plus; Vidoran Smart; Vipro-G; Vipro-G; Xanda; *Ital.*: Magen-700; Novostatin; Taurovit; *Malaysia*: Appeton; *Philipp.*: Biomix; Ceegeefer†; Celermin†; Chlorvytol†; Crevytin†; Dreamvite; Ener A Plus; Enersel; Enouvim; EZ-Grow; Flexivit; Folanerve; Healthy Kidz; Hi-Smart Teens; Hi-Smart; Kiddie Estamin; Kiddirel; Lexivit; Lysadam Plus; Lysmix; Memorx IQ Plus; Multigrow; Natalsure; Natalwiz; Nerveplex; Nerveplex; Neurosmart; Nutrazinc; Nutri 10; Nutricaire; Nutrigrow Plus; Nutrigrow†; Nutrigrow; Nutrilin; Nutrotal; OB Max; OB Smart SG; Onevit; Optigrow; Pediafortan Forte-GE; Pediafortan Forte; Propan TLC; Pryce-Kidz; Regeron Vita with Chlorella; Regeron Vita with Chlorella; Rejuvon; Restor-F; Restor; Strevit; Supranutrol; Syplex; TLC Vita; Tropicee Plus; Ultravit-TL; United American Tiki Tiki Star; Vigorvit; Vita SL Plus; Vitakids; Vitaplex; Vitazinc; *Port.*: Detoxergon; *Rus.*: Genferon (Генферон); Genferon Light (Генферон Лайт); *Singapore*: Growee†; Nutrivision†; *UK*: Boost; *Ukr.*: Cratal (Кратал); Oko-Health (Око-хелс); PM Sirin (ПМ Сирин); *USA*: Diabetiks.

Teriflunomide *(USAN, rINN)*

A-771726; HMR-1726; RS-61980; SU-0020; Teriflunomida; Tériflunomide; Teriflunomidum; Терифлуномид.

(*Z*)-2-Cyano-α′α′α-trifluoro-3-hydroxy-*p*-crotonotoluidide.

$C_{12}H_9F_3N_2O_2$=270.2

CAS — 108605-62-5; 163451-81-8.

UNII — 1C058IKG3B.

Uses and Administration

Teriflunomide is a pyrimidine synthesis inhibitor that acts as an immunomodulator with anti-inflammatory and immunosuppressant properties. It is used in the treatment of relapsing forms of multiple sclerosis (p. 996.3). An oral dose of 7 or 14 mg is given once daily.

Teriflunomide is the major active metabolite of leflunomide (p. 81.3).

References.

1. O'Connor PW, *et al.* Teriflunomide Multiple Sclerosis Trial Group. University of British Columbia MS/MRI Research Group. A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology* 2006; **66:** 894–900.
2. O'Connor P, *et al.* TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; **365:** 1293–1303.
3. Confavreux C, *et al.* Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Multiple Sclerosis* 2012; **18:** 1278–89.
4. Miller AE, *et al.* Teriflunomide Multiple Sclerosis Trial Group. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. *Multiple Sclerosis* 2012; **18:** 1625–32.
5. Freedman MS, *et al.* Teriflunomide Multiple Sclerosis Trial Group and the MRI Analysis Center. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. *Neurology* 2012; **78:** 1877–85.

Adverse Effects and Precautions

As for Leflunomide, p. 82.1. Hyperkalaemia has also been reported in patients given teriflunomide.

Interactions

Interactions for teriflunomide are expected to be similar to those for leflunomide (see p. 82.3). Studies have also suggested that teriflunomide may be an inhibitor of the cytochrome P450 isoenzyme CYP2C8 and a weak inducer of CYP1A2.

For reference to the effect of teriflunomide on warfarin, see Immunosuppressants, under Warfarin, p. 1534.2.

Pharmacokinetics

Teriflunomide is absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 and 4 hours after an oral dose. It is mainly distributed in plasma and is more than 99% bound to plasma proteins. Teriflunomide is mostly eliminated as unchanged drug in the bile and as metabolites in the urine. It is thought to undergo enterohepatic recycling and has an elimination half-life of about 18 to 19 days after repeated oral doses; it takes about 3 months to reach steady-state concentrations.

Teriflunomide is distributed into the milk of *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Aubagio.

Terlipressin *(BAN, USAN, rINN)* ⊗

Terlipresina; Terlipressine; Terlipressinum; Triglycyl-lysine-vasopressin; Терлипрессин.

N-[*N*-(*N*-Glycylglycyl)glycyl]lypressin; Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (4→9) disulphide.

$C_{52}H_{74}N_{16}O_{15}S_2$=1227.4
CAS — 14636-12-5.
ATC — H01BA04.
ATC Vet — QH01BA04.
UNII — 7ZSX49W53P.

Terlipressin Acetate (BANM, rINNM) ⊗

Acetato de terlipresina; Terlipresin Asetat; Terlipresina, acetato de; Terlipressiinisetaatti; Terlipressin Diacetate; Terlipressinacetat; Terlipressine, Acétate de; Terlipressini Acetas; Терлипрессина Ацетат.

$C_{52}H_{74}N_{16}O_{15}S_2,2C_2H_4O_2,5H_2O$=1437.6
ATC — H01BA04.
ATC Vet — QH01BA04.
UNII — 4U092XZF0K.

Uses and Administration

Terlipressin is an inactive prodrug that is slowly converted in the body to lypressin, and has the general physiological actions of vasopressin (p. 2643.1). It is given as the acetate although doses may be expressed as the base; 1 mg of terlipressin acetate is equivalent to about 0.85 mg of terlipressin.

Terlipressin acetate is used to control bleeding oesophageal varices and is given by intravenous injection in doses of 1 to 2 mg, followed by 1 to 2 mg every 4 to 6 hours if necessary, until bleeding is controlled, for up to 72 hours.

In the treatment of hepatorenal syndrome type 1 (see below) the recommended starting dose is the equivalent of 0.85 mg of terlipressin every 6 hours by slow intravenous bolus injection. If, after 3 days, serum creatinine has not decreased by at least 30% from its baseline value, the dose can be increased to 1.7 mg every 6 hours; however, such increases are not advised in patients with severe pre-existing cardiovascular disease or an ongoing significant adverse effect such as pulmonary oedema or ischaemia. Treatment should be continued until about 2 days after the patient achieves a reversal of hepatorenal syndrome, as indicated by a serum creatinine concentration of ≤132.6 micromoles/litre. The initial course of treatment may be continued for up to 2 weeks.

Terlipressin is under investigation in the treatment of shock.

Hepatorenal syndrome. Terlipressin given intravenously is used in the treatment of hepatorenal syndrome, a form of renal impairment associated with cirrhosis of the liver. A literature review[1] of clinical studies and meta-analyses found evidence to suggest that renal function was improved in patients with hepatorenal syndrome when treated with terlipressin; a reduction in mortality was also shown in some but not all studies. However, relapse was noted in one study after terlipressin was stopped and adverse effects have occurred. In particular, systemic ischaemic effects can be a problem even in patients without a known risk of cardiovascular disease. The authors considered that terlipressin was a reasonable option for improving renal function before liver transplantation; however, definitive recommendations could not be given.

1. Mazur JE, *et al.* Terlipressin in hepatorenal syndrome. *Ann Pharmacother* 2011; 45: 380–7.

Shock. Terlipressin has vasopressor effects and has been tried[1,2] in the management of septic shock (p. 1279.3). In a group of 8 patients who could not be adequately managed with conventional vasopressor therapy, an intravenous bolus of terlipressin 1 to 2 mg produced a progressive increase in mean arterial pressure over 10 to 20 minutes that was sustained for at least 5 hours, allowing reduction or cessation of noradrenaline.[3] Similar beneficial results have also been reported by others.[4,5] The use of a continuous infusion of terlipressin (500 micrograms/hour for 6 hours followed by half this dose for a further 12 hours) has been described in one case and appeared to be effective.[6] There are also reports[7,8] of a total of 20 children treated with bolus doses of 20 micrograms/kg every 4 hours for up to 72 hours. Terlipressin has also been used with some success as rescue therapy in doses of 7 to 20 micrograms/kg in children with extremely low cardiac output following open-heart surgery.[9]

1. Delmas A, *et al.* Clinical review: vasopressin and terlipressin in septic shock patients. *Crit Care* 2005; 9: 212–22.
2. Pesaturo AB, *et al.* Terlipressin: vasopressin analog and novel drug for septic shock. *Ann Pharmacother* 2006; 40: 2170–7.
3. O'Brien A, *et al.* Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; 359: 1209–10.
4. Morelli A, *et al.* Effects of terlipressin on systemic and regional haemodynamics in catecholamine-treated hyperkinetic septic shock. *Intensive Care Med* 2004; 30: 597–604.
5. Leone M, *et al.* Terlipressin in catecholamine-resistant septic shock patients. *Shock* 2004; 22: 314–19.
6. Jolley DH, *et al.* Terlipressin infusion in catecholamine-resistant shock. *Anaesth Intensive Care* 2003; 31: 560–4.
7. Rodríguez-Núñez A, *et al.* Terlipressin for catecholamine-resistant septic shock in children. *Intensive Care Med* 2004; 30: 477–80.
8. Rodríguez-Núñez A, *et al.* Rescue treatment with terlipressin in children with refractory septic shock: a clinical study. *Crit Care* 2006; 10: R20. Available at: http://ccforum.com/content/10/1/R20 (accessed 28/05/09)
9. Matok I, *et al.* Terlipressin for children with extremely low cardiac output after open heart surgery. *Ann Pharmacother* 2009; 43: 423–9.

Variceal haemorrhage. Systematic review has indicated[1] that terlipressin is effective in the management of acute oesophageal variceal haemorrhage (see under Monoethanolamine, p. 2563.1), and reduces the relative risk of mortality by about one-third. Differences in efficacy from other therapies could not be conclusively shown. Comparison of a regimen of terlipressin given by intravenous bolus injection, plus glyceryl trinitrate given sublingually, with balloon tamponade in variceal bleeding has suggested similar efficacy.[2] However, tamponade was successful in all patients that were previously unresponsive to terlipressin plus glyceryl trinitrate whereas this drug combination failed in all patients previously unresponsive to tamponade. A comparison of terlipressin and endoscopic injection sclerotherapy found them to be equally effective for the control of acute variceal bleeding.[3]

1. Ioannou GN, *et al.* Terlipressin for acute esophageal variceal hemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
2. Fort E, *et al.* A randomized trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute variceal hemorrhage. *Hepatology* 1990; 11: 678–81.
3. Escorsell À, *et al.* Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology* 2000; 32: 471–6.

Adverse Effects, Treatment, and Precautions

As for Vasopressin, p. 2643.3.

The pressor and antidiuretic effects of terlipressin are reported to be less marked than those of vasopressin.

Effects on electrolytes. A report of hypokalaemia in a patient receiving terlipressin.[1]

1. Stéphan F, Paillard F. Terlipressin-exacerbated hypokalaemia. *Lancet* 1998; 351: 1249–50.

Effects on the skin. Ischaemic skin necrosis developed in 3 patients several days after starting terlipressin treatment.[1] Skin lesions developed on the abdomen and lower limbs, which are not typical areas for ischaemia related to vasoconstrictors, and the authors concluded that obesity and venous insufficiency in these patients put them at particular risk.

1. Donnellan F, *et al.* Ischaemic complications of Glypressin in liver disease: a case series. *Br J Clin Pharmacol* 2007; 64: 550–2.

Interactions

As for Vasopressin, p. 2644.2.

Pharmacokinetics

Following intravenous injection, terlipressin shows a biphasic decline in plasma concentrations, with distribution and elimination half-lives of between about 8 to 12 minutes and 50 to 80 minutes, respectively. Terlipressin is metabolised by tissue peptidases resulting in the slow release of lypressin; maximum plasma concentrations are reached after about 2 hours. Terlipressin is almost completely metabolised in the kidneys and liver, with less than 1% of terlipressin and less than 0.1% of lypressin excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Glypressin; *Austral.*: Lucassin; *Austria*: Glycylpressin; Haemopressin; *Belg.*: Glypressin; Variquel; *China*: Glypressin (可利新); Remestyp (安立孚); *Cz.*: Glypressin; Remestyp; *Denm.*: Glypressin; Glypressine; Variquel; *Fin.*: Glypressin; Stemflova; *Fr.*: Glypressine; Haemopressin; *Ger.*: Glycylpressin; Haemopressin; *Gr.*: Glypressin; *Hong Kong*: Glypressin; *Hung.*: Glypressin; *Irl.*: Glypressin; Haemopressin; *Israel*: Glypressin; *Ital.*: Glipressina; *Malaysia*: Glypressin; *Mex.*: Glyverase; *Neth.*: Glypressin; Haemopressin; *Norw.*: Glypressin; Stemflova; *NZ*: Glypressin; *Philipp.*: Glypressin; *Pol.*: Glypressin; Remestyp; *Port.*: Glypressine; *Rus.*: Remestyp (Реместип); *Singapore*: Glypressin; *Spain*: Glypressin; Variquel; *Swed.*: Glypressin; Variquel; *Switz.*: Glypressine; Haemopressin; *Thai.*: Glypressin; *Turk.*: Glypressin; *UK*: Glypressin; Variquel; *Ukr.*: Glypressin (Глипрессин); Remestip (Реместип).

Terpineol

Терпинеол.

$C_{10}H_{18}O$=154.3
CAS — 8000-41-7 (terpineol); 98-55-5 (α-terpineol).
UNII — R53Q4ZWC99 (terpineol); 21334LVV8W (α-terpineol); 21M14KDA67 (l-α-terpineol); 5PH9U7XEWS (gamma-terpineol).

Pharmacopoeias. In *Br.*

BP 2014: (Terpineol). A mixture of structural isomers in which α-terpineol predominates. It is a colourless, slightly viscous liquid which may deposit crystals; it has a pleasant characteristic odour. Very slightly soluble in water; freely soluble in alcohol (70%); soluble in ether.

Profile

Terpineol has disinfectant and solvent properties. It is used with other volatile agents in preparations for respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Atomo Desinflamante Familiar; Atomo Desinflamante G; Atomo Desinflamante; Bronco Etersan; Di-Neumobron; Previnfec; *Braz.*: Bromil Grip†; Bromil; Bromil; Penetro; *Cz.*: Coldastop; *Fr.*: Nazinette du Docteur Gilbert; Pectodermet†; Valda†; *India*: Aerway; Coriminic-Vaporise; Dettol Obstetric; Dettol; Easi Breathe; Pairgenol; Genvol Plus; Karvol Plus; Kolq Inhalant; Sinarest Vapocaps; *Irl.*: Karvol; *Israel*: Gargol; Karvol; Rexitol†; *Ital.*: Calyptol; Rikospray; Skab 2†; *Mon.*: Calyptol; *NZ*: Tixylix Chest Rub; *S.Afr.*: AF; Karvol†; *Singapore*: Karvol; *Spain*: Caltoson Balsamico†; Eupnol; *Switz.*: Perskindol Classic; *UK*: Chymol; Jacksons Mentholated Balm; Karvol; Nowax.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution.

Tesmilifene Hydrochloride (USAN, rINNM)

BMS-217380-01; BMY-33419; DPPE; Hidrocloruro de tesmilifeno; Tesmilifène, Chlorhydrate de; Tesmilifeni Hydrochloridum; Tesmilifeno, hidrocloruro de; Тезмилифена Гидрохлорид.

2-[(α-Phenyl-*p*-tolyl)oxy]triethylamine hydrochloride; *N,N*-Diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine hydrochloride.

$C_{19}H_{25}NO,HCl$=319.9
CAS — 98774-23-3 (tesmilifene); 92981-78-7 (tesmilifene hydrochloride).
UNII — 1U4B477260.

Profile

Tesmilifene hydrochloride is an intracellular histamine antagonist that appears to augment the antineoplastic activity of drugs such as the anthracyclines and taxanes. It is under investigation for the treatment of various cancers, including hormone-refractory cancer of the prostate and gastric and hepatic cancers.

References.

1. Reyno L, *et al.* Phase III study of N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA19. *J Clin Oncol* 2004; 22: 269–76.
2. Raghavan D, *et al.* Phase II trial of tesmilifene plus mitoxantrone and prednisone for hormone refractory prostate cancer: high subjective and objective response in patients with symptomatic metastases. *J Urol (Baltimore)* 2005; 174: 1808–13.

Tetrabenazine (BAN, rINN)

Ro-1-9569; Tetrabenatsiini; Tetrabenazin; Tetrabenazina; Tétrabénazine; Tetrabenazinum; Тетрабеназин.

1,3,4,6,7,11b-Hexahydro-3-isobutyl-9,10-dimethoxybenzo-[*a*] quinolizin-2-one.

$C_{19}H_{27}NO_3$=317.4
CAS — 58-46-8.
ATC — N07XX06.
ATC Vet — QN07XX06.
UNII — Z9O08YRN8O.

Uses and Administration

Tetrabenazine is used in the management of movement disorders including chorea (p. 1029.3), ballism (p. 1029.3), dystonias (p. 903.3), tardive dyskinesia (see under Extrapyramidal Disorders, p. 1049.2), and similar symptoms of CNS dysfunction.

For the treatment of chorea, ballism, and other organic CNS movement disorders, a starting oral dose of 12.5 to 25 mg up to three times daily has been recommended. The dose may be gradually increased by 12.5 to 25 mg every 3 or 4 days according to response up to a maximum of 200 mg daily. If the patient does not respond within 7 days of receiving the maximum dose further treatment with tetrabenazine is unlikely to be of benefit.

In the USA, the following doses are recommended for Huntington's chorea. A starting dose of 12.5 mg daily given in the morning is recommended, which may be increased after one week to 25 mg daily given in 2 divided doses. The dose may then be gradually increased by 12.5 mg daily at weekly intervals according to response. Daily doses greater than 37.5 to 50 mg should be given in 3 divided doses with a maximum single dose of 25 mg. Patients who appear to need doses above 50 mg daily should be genotyped for the cytochrome P450 isoenzyme CYP2D6: doses in extensive or intermediate CYP2D6 metabolisers may be increased by 12.5 mg daily at weekly intervals according to response up to a maximum daily dose of 100 mg given in 3 divided doses with a maximum single dose of 37.5 mg; in poor CYP2D6 metabolisers, the maximum daily dose is 50 mg given in 3 divided doses with a maximum single dose of 25 mg.

For moderate to severe tardive dyskinesia, a dose of 12.5 mg daily is recommended initially, subsequently titrated according to response.

For doses in hepatic impairment, see below.

Reviews.

1. Fasano A, Bentivoglio AR. Tetrabenazine. *Expert Opin Pharmacother* 2009; 10: 2883–96.

Administration in hepatic impairment. UK licensed product information for tetrabenazine recommends that an initial oral dose of 6.25 mg up to three times daily, and a slower increase in dose, should be used in patients with mild to moderate hepatic impairment. Information is lacking about use in patients with severe impairment and so caution is advised.

Extrapyramidal disorders. In a long-term study[1] of the use of tetrabenazine in 400 patients with movement disorders, the best responses seemed to be in tardive dyskinesia, tardive dystonia, and Huntington's disease but benefit was also obtained in some patients with idiopathic dystonia, segmental myoclonus, and Tourette's syndrome. Others have commented that in severe dystonia unresponsive to other drugs a combination of tetrabenazine with trihexyphenidyl and pimozide is sometimes effective.[2] Tetrabenazine significantly reduced chorea in ambulatory patients with Huntington's disease in a small 12-week randomised placebo-controlled study.[3] It was well tolerated, although there was a significant increase in reports of drowsiness and insomnia, which generally resolved with adjustment of doses.

1. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997; 48: 358–62.
2. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; 300: 139–44.
3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; 66: 366–72.

Adverse Effects

Drowsiness is the most frequent adverse effect of tetrabenazine. Orthostatic hypotension, symptoms of extrapyramidal dysfunction, gastrointestinal disturbances, and depression may also occur. Neuroleptic malignant syndrome and parkinsonism have been reported rarely. Overdosage has produced sedation, sweating, hypotension, and hypothermia.

Effects on mental function. Depression is well documented as an adverse effect of tetrabenazine, and occurs in about 15% of patients; it has been reported to respond to reboxetine.[1] Florid psychiatric symptoms such as panic attacks and obsessive-compulsive symptoms may be precipitated or exacerbated by tetrabenazine.[2]

1. Schreiber W, *et al.* Reversal of tetrabenazine induced depression by selective noradrenaline (norepinephrine) reuptake inhibition. *J Neurol Neurosurg Psychiatry* 1999; 67: 550.
2. Bruneau MA, *et al.* Catastrophic reactions induced by tetrabenazine. *Can J Psychiatry* 2002; 47: 683.

Extrapyramidal disorders. Dysphagia and choking were associated with tetrabenazine in the treatment of Huntington's chorea.[1] Fatal pneumonia, probably as a consequence of aspiration, had also been reported.

1. Snaith RP, Warren H de B. Treatment of Huntington's chorea with tetrabenazine. *Lancet* 1974; i: 413–14.

Overdosage. A patient who swallowed about 1 g (40 tablets) of tetrabenazine became drowsy 2 hours later and marked sweating occurred.[1] Her state of consciousness improved after 24 hours and she talked rationally and gained full control of micturition after 72 hours.

1. Kidd DW, McLellan DL. Self-poisoning with tetrabenazine. *Br J Clin Pract* 1972; 26: 179–80.

Precautions

Tetrabenazine is contra-indicated in actively suicidal patients or in cases of untreated or inadequately treated depression. It should be given with caution to patients with hepatic impairment. Tetrabenazine may exacerbate the symptoms of parkinsonism. It may cause drowsiness; affected patients should not drive or operate machinery.

Interactions

Tetrabenazine may diminish the effects of levodopa and exacerbate the symptoms of parkinsonism. Tetrabenazine should not be started until at least 20 days after stopping reserpine in order to avoid major depletion of serotonin and noradrenaline in the CNS. Use of tetrabenazine immediately after a course of an MAOI may lead to confusion, restlessness, and disorientation; tetrabenazine should not be given with, or within 14 days of stopping, such therapy.

Pharmacokinetics

Absorption of tetrabenazine is poor and erratic after oral doses. It appears to be extensively metabolised by first-pass metabolism; the cytochrome P450 isoenzyme CYP2D6 has a significant role in the metabolism of tetrabenazine and this may affect doses (see Uses and Administration, p. 2627.3). The major metabolite of tetrabenazine, hydroxytetrabenazine, which is formed by reduction, is reported to be as active as the parent compound. Tetrabenazine is excreted in the urine mainly in the form of metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Nitoman; *Cz.*: Tetmodis; *Denm.*: Nitoman; Tetmodis; *Fin.*: Tetmodis; *Fr.*: Xenazine; *Ger.*: Nitoman; Tetmodis; *Gr.*: Xenazine; *India*: Revocon; *Irl.*: Nitoman; Tetmodis; *Israel*: Xenazine; *Ital.*: Xenazina; *Jpn*: Choreazine; *Neth.*: Tetmodis; Xenazine; *NZ*: Xenazine; *Port.*: Nitoman; Revocon; *Spain*: Nitoman; *Swed.*: Tetmodis; Xenazine; *Switz.*: Xenazine; *UK*: Revocon; Tetmodis; Xenazine; *USA*: Xenazine.

Tetrachlorodecaoxide

TCDO; Tetrachlorodecaoxygen Anion Complex; Tetraclorodecaóxido; WF-10.

Cl_4O_{10}=301.8

CAS — 92047-76-2.

Profile

Tetrachlorodecaoxide is a water-soluble anion complex containing oxygen in a chlorite matrix. Active oxygen is only released in the presence of biological material. It has been applied as a solution for the stimulation of wound healing, and has been tried in the management of mucositis.

Mucositis. Benefit has been reported from the use of tetrachlorodecaoxide in the management of mucositis induced by chemotherapy[1] or radiotherapy,[2] although it appears to be minor.[1] Benefit has also been reported in reducing recurrence of radiation-induced haemorrhagic cystitis.[3]

1. Malik IA, *et al.* A double-blind, placebo-controlled, randomized trial to evaluate the role of tetrachlorodecaoxide in the management of chemotherapy-induced oral mucositis. *J Pain Symptom Manage* 1997; 14: 82–7.
2. Penpattanagul S. Reduced incidence and severity of acute radiation mucositis by WF10 (IMMUNOKINE) as adjunct to standard of cure in the management of head & neck cancer patients. *J Med Assoc Thai* 2007; 90: 1590–600.
3. Veerasarn V, *et al.* Reduced recurrence of late hemorrhagic radiation cystitis by WF10 therapy in cervical cancer patients: a multicenter, randomized, two-arm, open-label trial. *Radiother Oncol* 2004; 73: 179–85.

Wounds. Tetrachlorodecaoxide was reported to promote wound healing compared with saline in a double-blind study of 271 patients,[1] but a smaller study failed to show any benefit over glycerol.[2]

1. Hinz J, *et al.* Rationale for and results from a randomised, double-blind trial of tetrachlorodecaoxygen anion complex in wound healing. *Lancet* 1986; i: 825–8.
2. Hughes LE, *et al.* Failure of tetrachlorodecaoxygen anion complex to assist wound healing. *Lancet* 1989; ii: 1271.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Oxoferin; *Indon.*: Oxoferin; *Port.*: Oxoferin; *Thai.*: Immunokine; Oxoferin; *Venez.*: Oxoferin.

Tetramethylammonium Iodide

Tetrametilamonio, ioduro de; Иодид Тетраметиламмония.

$C_4H_{12}IN$=201.1

CAS — 75-58-1.

Profile

Tetramethylammonium iodide is a quaternary ammonium compound that has been used for the emergency disinfection of drinking water. It has also been used for its ganglion-blocking properties.

Thallium Acetate

Talio, acetato de; Thallous Acetate.

$C_2H_3O_2Tl$=263.4

CAS — 7440-28-0 (thallium); 563-68-8 (thallium acetate); 7446-18-6 (thallium sulfate).

Uses and Administration

Thallium acetate was formerly used orally for depilation in ringworm and as an ingredient of depilatory creams but both systemic and local treatments have caused deaths, and it is no longer used for such purposes. It has also been used as a rodenticide and insecticide; thallium sulfate has been used similarly. The use of thallium salts is strictly regulated in many countries. However, use in industry could still constitute a hazard. Cases of malicious poisoning still occur occasionally.

Adverse Effects

Thallium salts are toxic when inhaled, ingested, or absorbed through the skin. Symptoms of poisoning may appear within 12 to 24 hours of a single toxic dose and include severe abdominal pain, nausea and vomiting, diarrhoea, gastrointestinal haemorrhage, salivation, metallic taste, paralytic ileus, pancreatic damage, and in severe cases cardiovascular collapse, tremors, delirium, convulsions, paralysis, and coma, leading to death in 1 to 2 days. However, the acute reaction may subside, to be followed within about 10 days by the development of neurological effects including paraesthesia, myalgia, myopathy, motor neuropathy, and visual disturbances due to optic neuropathy, psychosis, delirium, convulsions, and other signs of encephalopathy, tachycardia, hypertension, skin eruptions, and hepatorenal injury. Recovery from neurological damage is slow and may be incomplete. Alopecia occurs within 15 to 20 days; stomatitis may also develop. Death may result from respiratory failure; patients are also predisposed for several weeks to cardiac arrhythmias and sudden death. Fatalities have occurred after ingestion of 3 to 10 g of thallium compounds by adults and 85 to 89 mg/kg by children.

Smaller repeated doses are also toxic, with symptoms appearing over several weeks. Constipation is a common feature of less severe poisoning.

Poisoning. References.

1. Moeschlin S. Thallium poisoning. *Clin Toxicol* 1980; 17: 133–46.
2. Heyl T, Barlow RJ. Thallium poisoning: a dermatological perspective. *Br J Dermatol* 1989; 121: 787–92.
3. Luckit J, *et al.* Thrombocytopenia associated with thallium poisoning. *Hum Exp Toxicol* 1990; 9: 47–8.
4. Moore D, *et al.* Thallium poisoning. *BMJ* 1993; 306: 1527–9.
5. Tabandeh H, Thompson GM. Visual function in thallium toxicity. *BMJ* 1993; 307: 324.
6. Questel F, *et al.* Thallium-contaminated heroin. *Ann Intern Med* 1996; 124: 616.
7. Tromme I, *et al.* Skin signs in the diagnosis of thallium poisoning. *Br J Dermatol* 1998; 138: 321–5.
8. Hoffman RS. Thallium poisoning during pregnancy: a case report and comprehensive literature review. *J Toxicol Clin Toxicol* 2000; 38: 767–75.
9. Misra UK, *et al.* Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J* 2003; 79: 103–5.
10. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; 22: 29–40.
11. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; 38: 1509–14.
12. Kuo H-C, *et al.* Acute painful neuropathy in thallium poisoning. *Neurology* 2005; 65: 302–4.
13. CDC. Thallium poisoning from eating contaminated cake—Iraq, 2008. *MMWR* 2008; 57: 1015–18.

Treatment of Adverse Effects

Gastric lavage should be considered if the patient presents within 1 hour of acute ingestion. Intensive supportive therapy is necessary.

Attempts have been made to increase the faecal and urinary excretion of thallium. A suspension of activated charcoal has been given to reduce intestinal absorption and enteric recycling. Prussian blue (p. 1572.3) given orally or via a nasogastric tube is also used routinely. A purgative such as mannitol may be required with either activated charcoal or Prussian blue as constipation is common in severe thallium toxicity. Giving potassium chloride orally may mobilise thallium from the tissues but is hazardous, especially if given during the early stage as signs of poisoning may be aggravated. Traditional chelation therapy is not generally recommended for thallium poisoning.

Haemoperfusion, haemodialysis, or peritoneal dialysis have been reported to be effective in eliminating absorbed thallium, although clinical benefit is doubtful.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Ger.*: Hautfunktionstabletten N; Hautfunktionstropfen N; *Neth.*: Cutis comp.

Theodrenaline Hydrochloride

(BANM, rINNM) ⊗

H-8352; Hidrocloruro de teodrenalina; Noradrenaline Theophylline Hydrochloride; Teodrenalina, hidrocloruro de; Théodrénaline, Chlorhydrate de; Theodrenalini Hydrochloridum; Теодреналина гидрохлорид.

7-[2-(3,4,β-Trihydroxyphenethylamino)ethyl]theophylline hydrochloride.

$C_{17}H_{21}N_5O_5.HCl$=411.8

CAS — 13460-98-5 (theodrenaline); 2572-61-4 (theodrenaline hydrochloride).

ATC — C01CA23.

ATC Vet — QC01CA23.

Profile

Theodrenaline is mainly used as the hydrochloride in preparations with cafedrine promoted for the treatment of hypotension. This preparation has been subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Akrinor†; *Fr.*: Praxinor; *Ger.*: Akrinor; *Indon.*: Akrinor; *S.Afr.*: Akrinor.

Thioctic Acid

Acide thioctique; Ácido α-lipoico; Acidum thiocticum; Alpha Lipoic Acid; Kwas tioktynowy; Kyselina thioktová; Lipoic Acid; α-Liponic Acid; Thioctsäure; Tióctico, ácido; Тиоктовая Кислота.

5-(1,2-Dithiolan-3-yl)valeric acid.

$C_8H_{14}O_2S_2$=206.3

CAS — 62-46-4.

ATC — A16AX01.

ATC Vet — QA16AX01.

UNII — 73Y7P0K73Y.

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

Ph. Eur. 8: (Thioctic Acid). A yellow, crystalline powder. M. p. about 61 degrees. Very slightly soluble in water; very soluble in dimethylformamide; freely soluble in methyl alcohol. Protect from light.

USP 36: (Alpha Lipoic Acid). M.p. 60.0 degrees to 62.0 degrees.

Profile

Thioctic acid is used for its antoxidant effects in the treatment of diabetic neuropathy. It has been tried in the treatment of liver dysfunction, subacute necrotising encephalopathy, and pain. Beneficial results have been claimed in amanitin poisoning after ingestion of the mushroom *Amanita phalloides*, but such use is controversial (see Amanita Phalloides under Poisonous Mushrooms or Toadstools, p. 2565.3). Ethylenediamine thioctate, sodium thioctate, thioctic acid amide (thioctamide), and trometamol thioctate have been used similarly.

Adverse effects. Severe cholestatic hepatitis has been reported[1] in a patient who was taking thioctic acid for the symptomatic treatment of diabetic neuropathy; symptoms resolved when the drug was stopped and recurred on rechallenge.

Insulin auto-immune syndrome has been associated with the use of thioctic acid as a dietary supplement.[2]

1. Ridruejo E, *et al.* Thioctic acid-induced acute cholestatic hepatitis. *Ann Pharmacother* 2011; 45: e43.
2. Bresciani E, *et al.* Insulin autoimmune syndrome induced by α -lipoic acid in a Caucasian woman: case report. *Diabetes Care* 2011; 34: e146.

Pharmacokinetics. References.

1. Teichert J, *et al.* Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage renal disease. *J Clin Pharmacol* 2005; 45: 313–28.

Use in diabetic neuropathy. A review[1] and meta-analysis[2] of randomised controlled studies concluded that thioctic acid 600 mg daily given intravenously for 3 weeks reduced the symptoms of diabetic neuropathy (p. 465.2); however, the clinical relevance of improvements seen after oral dosage of 600 mg daily for up to 5 weeks is unclear.[2]

1. Mcilduff CE, Rutkove SB. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. *Ther Clin Risk Manag* 2011; 7: 377–85.
2. Mijnhout GS, *et al.* Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol* 2012; 2012: 456279.

Use in pain. Thioctic acid has been tried in the treatment of pain (see Choice of Analgesic, p. 4.2) of various causes including sciatic pain following herniated disc,[1] back pain,[2] and burning mouth syndrome.[3]

1. Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study. *Clin Drug Investig* 2008; 28: 495–500.
2. Ranieri M, *et al.* The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: effect on health-related quality of life. *Int J Immunopathol Pharmacol* 2009; 22 (suppl): 45–50.
3. López-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of burning mouth syndrome: a randomized, double-blind, placebo controlled trial. *Med Oral Patol Oral Cir Bucal* 2011; 16: e635–e640.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biletan; Ciagen; Neurotioct; Neutracol; Sigmus; Tioctan; Tioctic; Tiodrix; Tioneurol; *Austria*: Thioctacid; Tioctan; *Braz.*: Thioctacid; *China*: Alpha-Lipon (奥力宝); Ao Tian Li (奥天利); *Cz.*: Thioctacid; Thiogamma; *Ger.*: Alpha-Lipogamma; Alpha-Lipon†; alpha-Vibolex; Biomolipon†; Neurium†; Pleomix-Alpha; Thioctacid; Thiogamma; Tromlipon; Verla-Lipon†; Vitatrans†; *Hong Kong*: Thiogamma; *Hung.*: Thioctacid; Thiogamma; *India*: Ala; Aladin; Cobal Forte; Lipocid; *Indon.*: Alanox; Mecola Forte; *Ital.*: Patiox; Tiobec Crema; *Mex.*: Thioctacid; *Pol.*: Neurex†; Neurolipon; Thiogamma; *Port.*: Thioctacid; *Rus.*: Berlithion (Берлитион); Espa-Lipon (Эспа-липон); Lipothioxon (Липотиоксон); Octolipen (Октолипен); Thioctacid (Тиоктацид); Thiogamma (Тиогамма); Thiolepta (Тиолепта); Thiolipon (Тиолипон); *Thai.*: Lipoicin; *Ukr.*: Alfa-Lipon (Альфа-Липон); Berlithion (Берлитион); Dialipon (Диалипон); Espa-Lipon (Эспа-Липон); Thioctacid (Тиоктацид); Thiogamma (Тиогамма).

Multi-ingredient Preparations. *Arg.*: Biletan Enzimatico; Carbogasol Digestivo; Cellasene Gold; Cistidac; Co-Tioctan; Nervomax TB12; *Austral.*: Gluco Support; Tresos B PluSe; Womens Multi; *Canad.*: Trim-Fit†; *Fr.*: Glycontrol; *Hong Kong*: Lipochol; *India*: Acmic-Alpha; Ala-Plus; Alcrin-M; Alcrin; Alfariz; Almecol-B; Almecol; Alnacob-OD; Alpha Cad; Alphaneuron; Aluno-A; Ameco Plus; Ancob; Armet Plus; Barovit; Basix-AL; Beminal Forte; Bencoba; Benerv Forte; Benfage Forte; Benfo Forte; Berocin-CZ; Bigvin Plus; Cally Plus; Canbol Plus; Canmik; Catalyst; Cobaday-AV; Cobalip; Cobals Plus; Cobalvit Forte; Cobalvit Plus; Cobanerve Plus; Cobanerve; Cobasoft; Cobaver-OD; Coblona Plus; Colaba-B; Compicare-XL; Cumee-A; Dianerve; Dianuron; Diapill; Diavit; Doravit Forte; Ebiza-L; EC; Ecobal-Plus; Ecobal; Efcoba Forte; Efcoben; Elmecob Plus; Elneuro; Encentin-AM; Escobal; Eucobal; Exerge; Exox; Felicita-OD; Polirich-B; Fotia Plus; GCobal; GMab Plus; Hicobal; Hosit Plus; Humax-Alpha-R; Incobal Plus; Inerve; Keeneuron; Kefive Plus; L-Nit; Lameco Plus; Levineuro; Logic; Maconeuron-OD; Macraberin-M; Maddox-AL; Malzix; Marinol Alpha; Matilda; MCF-Max; Me Plus; Me-Plus; Mebal-Plus; Mecatin; Mecoba Alpha; Mecobal Plus; Mecobil-OD; Mecobion-OD; Mecobion; Mecoblend; Mecobyte; Mecocas; Mecoday Plus; Mecofol-A; Mecolife Plus; Mecompy-Forte; Meconerv Forte; Mecopil; Mecoriv Plus; Mecosa-OD; Mecovon; Medhamin Forte; Meganeuron; Mego-XL; Melcovit; Melvit; Memi; Menol-Plus; Met-Neurobion; Methico-AL; Methygard-OD; Mewin Forte; Mexivit; Mezen; Miko-OD; Mixovim; Moblo-AF; Moblo-Plus; MSA; Mycotop; Mycovit; N-Care Forte; Necob Plus; Nerjuwin; Nerve-O-Fitt; Nervic; Nervicin; Nervijen-D; Nervijen; Nervimax Plus; Nervion; Nervonic; Nervup Forte; Nervup-OD; Nervup-PG; Nervup; Nervz-B; Nervz; Nerwin-MD; Neucobal-Forte; Neuractin Forte; Neuroage; Neurocap-OD; Neurochek; Neuroforte; Neuroglow-B; Neuroglow; Neurokair; Neurolax-OD; Neuromed; Neurontin; Neuropill; Neurosoz-MC; Neurotop Plus; Neurozen; Neuvesca; Nexcob Plus; Nocad; Numeth; Nuro-M Plus; Nuro-M; Nurobest; Nuroclad-Plus; Nurokind Plus; Nuromax-OD; Nuromin; Nurosenz; Nurovir; Nurovole Plus; Nurozac-OD; Nuthyl-AL; Nutricobal Plus; Onerve; Oscob Forte; *Indon.*: Aldovas; Alicron; Aptivium Liver Support†; Canergy†; Cinula; Covitala; Fres Diab; Kapset; Mecola; Neofer; nu Qten Com; Proliva; Reliv†; Seloxy AA; Tiola; Univoxy; Vitala; *Ital.*: Alceclar†; Alfa Lip; Angiovein; Biophase Complex†; Biotad; Blunorm; Byodinoral; Depatox; Deproctol; Endoepatox; Lipoacid Combi; Neuralfa; Neuroptic; Osteolip Crema; Osteolip; Reumil; Rischiaril; Semel; Thiospot; Tiobec; Tiofort; Traumaven; Ulceclar; Vasobrain Plus; Visu-len; *Malaysia*: Olivenol livin' Youthful†; *Philipp.*: ALAnerv; Diamaxin; Illumina; *Port.*: Lipoacid Combi; Lipoacid; Thiospot; *Rus.*: Corylip (Корилип); Neurokomplit (Нейрокомплит); Selmevit (Селмевит); *S.Afr.*: Zeel; Zeel; *Singapore*: Essentials†; Olivenol Livin' Youthful; *Spain*: Policolinosil; *Thai.*: Lipochol; *UK*: Lacrima; Selene-Activ; *Ukr.*: Livonorm (Ливонорм); Oko-Health (Око-хелс); *USA*: Blood Sugar Balance; Cardio Tone; Corvita; Corvite Free; Daily Betic; Diabetiks.

Homoeopathic Preparations. *Canad.*: Hepar Compositum; Ubicoenzyme; *Cz.*: Zeel Salbe†; *Ger.*: Hepar comp; *Hung.*: Zeel; *Rus.*: Zeel T (Цель Т).

Pharmacopoeial Preparations

USP 36: Alpha Lipoic Acid Capsules; Alpha Lipoic Acid Tablets.

Thiomucase

C-84-04; Chondroitinsulphatase; Condroitinsulfatasa; EC 3.1.6.14; Tiomucasa; Тиомуказа.

Profile

Thiomucase is a mucopolysaccharidase with general properties similar to those of hyaluronidase, p. 2527.2, but which also depolymerises chondroitin sulfate. It has been given to assist the diffusion of local anaesthetic injections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Thiocase†.

Multi-ingredient Preparations. *Braz.*: Thiomucase.

Thiotriazoline

Tiotriazolin; Тиотриазолин.

Morpholine 5-methyl-1,2,4-triazoline-5-thioacetate.

Profile

Thiotriazoline is reported to have anti-ischaemic, membrane stabilising, and antoxidant actions. It is used as a hepatoprotectant in various liver disorders and as a protectant in cardiovascular and cerebrovascular disorders. It is also used locally as an anti-inflammatory for wounds and lesions of the skin and mucous membranes and for vaginal or rectal inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ukr.*: Dalmaxin (Далмаксин).

Multi-ingredient Preparations. *Ukr.*: Tiocetam (Тиоцетам); Tiodaron (Тиодарон).

Thiram *(USAN, rINN)*

NSC-1771; SQ-1489; Thirame; Thiramum; Tiram; Tiramo; TMT; TMTD; Тирам.

Tetramethylthiuram disulphide.

$C_6H_{12}N_2S_4$=240.4

CAS — 137-26-8.

ATC — P03AA05.

UNII — 0D771IS0FH.

Profile

Thiram, the methyl analogue of disulfiram (p. 2495.3), has antibacterial and antifungal activity. It has been applied topically as an aerosol in the treatment of wounds and other skin disorders. It has been used as a fungicide in agriculture, and in industry as a rubber accelerator. Occupational exposure to thiram may cause irritation of mucous membranes and skin.

Thorium Dioxide

Óxido de torio; Thorium Oxide; Torio, dióxido de; Диоксид Тория; Двуокись Тория.

ThO_2=264.0

CAS — 1314-20-1.

UNII — 9XA7X17UQC.

Profile

Colloidal solutions of thorium dioxide were formerly used as X-ray contrast media for examination of the liver and spleen, for arteriography, and occasionally for outlining the cerebral ventricles. Its elimination is very slow and incomplete. It accumulates in the reticuloendothelial system, especially in the liver and spleen. As it is radioactive (half-life: 1.41 X 10^{10} years), this accumulation is dangerous and there is strong evidence that the ensuing prolonged exposure to its radiation is a contributing factor in the development of malignant diseases and blood disorders often 20 to 30 years after its use.

Thuja

Tuya; White Cedar; Туя Западная *(Thuja occidentalis).*

ATC Herb — HD11AF5001 (Thuja occidentalis: herb).

UNII — 5HBV6WCE3N (Thuja occidentalis); 19RAD88E6O (Thuja occidentalis: bark); 0T0DQN8786 (Thuja occidentalis leaf); 1NT28V9397 (Thuja occidentalis leafy twig); 12958C0BR3 (Thuja occidentalis root).

Profile

Thuja consists of the fresh leaves and twigs of *Thuja occidentalis* (Cupressaceae). It is included in some topical preparations for warts and in herbal antiseptic preparations. It is also used in herbal preparations for respiratory-tract disorders.

The oil distilled from the leaves and twigs is known as thuja oil or cedar leaf oil. It has been included in preparations for inhalation for the relief of respiratory-tract symptoms and for external use but is generally considered to be too toxic for internal use. Cedar leaf oil should be distinguished from cedar wood oil, obtained from *Juniperus virginiana* (see p. 2472.3).

Homoeopathy

Thuja has been used in homoeopathic medicines under the following names: Thuja occidentalis; Thuja occ.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Thujaderm.

Multi-ingredient Preparations. *Austral.*: Esberitox N; Vicks Vaporub; *Austria*: Colda; Esberitox; Pe-Ce†; *Belg.*: Aporil; Vicks Vaporub; *Braz.*: Vick Vaporub; *China*: Esberitox (施保利通); *Fr.*: Nitrol†; Verrupan; Vicks Vaporub; *Ger.*: Esberitox; *Malaysia*: Esberitox N; *Pol.*: Esberitox N; *Port.*: Alpha Cade; Alphacedre; Erpecalm; *S.Afr.*: Vicks Vaporub†; *Spain*: Arkoresp†; Nitroina; *Swed.*: Esberitox; *Switz.*: Esberitop; Vicks Vaporub N; *Turk.*: Kataljin; Vicks Vaporub; *UK*: Fuerte; *Ukr.*: Esberitox (Эсберитокс); *USA*: Vicks Vaporub.

Homoeopathic Preparations. *Austral.*: Echine†; *Austria*: Echinacea-Cosmoplex; Gracil; Mandragora Med Complex; Sensicare; Spigelon; Thuja Med Complex; *Canad.*: Acne; Adrisin†; Calnor†; Candida Yeast Relief; Cutisitum†; Detox L37; Earache; Echinacea Compositum; Formula CA 205†; Homeo-Form C†; Homeo-Form CA†; Homeo-Form SI†; Homeo-Form T†; Lympatox; Nixotinex; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Sorinoheel; Spigelon†; Ubicoenzyme; War Complex†; *Chile*: Allium Compuesto; Bioactiv Q; Formula II Especial; Fucus Especial; *Cz.*: Galium; Ypsiloheel; *Fr.*: Juniperus Complexe No 6; Pulviplasmine†; Rhododendron Complexe No 42†; Sabal Serrulata Compose; Santalum Complexe No 30†; Sinuspax; Thuya Complexe No 37; Urtica Complexe No 82†; Verrulia; *Ger.*: Antimast TN†; Colchicum Complex; Entzundungstropfen; HanoFemin; Hanotoxin M; Hautfunktionstabletten N; Hautfunktionstropfen N; Hevertotox; Hewelymphon N†; Hewesoor N†; ISO-Augentropfen C; Jowidarmin; Juv 110; Lowe-Komplex Nr 5 Echinacea; Lymphaden; Muco-cyl L Ho-Len-Complex; Otofren; Pascoleucyn N; Pascoleucyn; Pflugerplex Lemna; Phonix Thuja-Lachesis spag; Prostata-Komplex N Ho-Fu-Complex†; Rapako comp; rheuma-loges; Rheuma-Pasc; Schleimhaut-Komplex L Ho-Fu-Complex; Sinuselect N; Sinusyx; Thuja N Oligoplex†; Thuja WA Oligoplex; Thujarell; Tondinel; Ulco-cyl L Ho-Len-Complex; Ypsiloheel N; *Hung.*: Spigelon; *Neth.*: Chavita 2; Chavita 5; Cutis comp; Habifac; Ricura; Thuyalite; *Rus.*: Berberis Comp (Барбарис Комп); Mastopol (Мастопол); Phytolacca-Plus (Фитолакка-Плюс); Ruta-Plus (Рута-Плюс); *Switz.*: Nelsons Sinusit†; Regenaplex Nr 28a; Regenaplex Nr. 31c; Spigelon.

Thymalfasin *(USAN, rINN)*

Thymalfasine; Thymalfasinum; Thymosin α1; Timalfasina; Тимальфазин.

CAS — 62304-98-7; 69521-94-4.

UNII — W0B22ISQ1C

Profile

Thymalfasin is a thymus hormone (p. 2631.1) found in thymosin fraction 5 (a crude thymus gland extract) but now produced by synthesis. Thymalfasin is used alone or with interferon as an immunomodulator for the treatment of chronic hepatitis B and is given by subcutaneous injection in a dose of 1.6 mg twice weekly for 6 to 12 months. The dose in patients who weigh less than 40 kg is 40 micrograms/kg. It is used with interferon for hepatitis C (p. 952.1). Thymalfasin is also used for chemotherapy-induced immunosuppression, and to enhance the efficacy of influenza vaccines in immunocompromised or elderly patients and of influenza and hepatitis B vaccines in chronic haemodialysis patients.

Thymalfasin is under investigation for hepatitis D and HIV infection and AIDS.

References.

1. Garaci E, *et al.* Sequential chemoimmunotherapy for advanced non-small cell lung cancer using cisplatin, etoposide, thymosin-α 1 and interferon-α 2a. *Eur J Cancer* 1995; 31A: 2403–5.
2. Rasi G, *et al.* Combination thymosin α_1 and lymphoblastoid interferon treatment in chronic hepatitis C. *Gut* 1996; 39: 679–83.
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4. Andreone P, *et al.* A randomized controlled trial of thymosin-α 1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody- and hepatitis B virus DNA-positive chronic hepatitis B. *Hepatology* 1996; 24: 774–7.
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8. Ancell CD, *et al.* Thymosin alpha-1. *Am J Health-Syst Pharm* 2001; 58: 879–85.
9. Andreone P, *et al.* Thymosin-alpha 1 plus interferon-alpha for naive patients with chronic hepatitis C: results of a randomized controlled pilot trial. *J Viral Hepatitis* 2004; 11: 69–73.
10. Sjogren MH. Thymalfasin: an immune system enhancer for the treatment of liver disease. *J Gastroenterol Hepatol* 2004; 19: S69–S72.
11. Rustgi V. Combination therapy of thymalfasin (thymosin-alpha 1) and peginterferon alfa-2a in patients with chronic hepatitis C virus infection who are non-responders to standard treatment. *J Gastroenterol Hepatol* 2004; 19: S76–S78.
12. Iino S, *et al.* The efficacy and safety of thymosin alpha-1 in Japanese patients with chronic hepatitis B: results from a randomized clinical trial. *J Viral Hepatitis* 2005; 12: 300–306.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Zadaxin; *China*: He Ri (和日); Ji Tai (基泰); Wan Yuan (万源); Xin Fu Tai (新扶泰); Zadaxin (日达仙); *Hong Kong*: Zadaxin; *Indon.*: Zadaxin; *Ital.*: Zadaxin; *Malaysia*: Zadaxin; *Mex.*: Zadaxin; *Philipp.*: Zadaxin; *Rus.*: Zadaxin (Задаксин); *Singapore*: Zadaxin; *Thai.*: Zadaxin.

Thyme

Common Thyme; Estremoncillo; French Thyme; Garden Thyme; Kakukkfű; Rubbed Thyme; Thym; Thymi Herba; Thymian; Timjami; Timjan; Timo; Tomello; Tomillo; Tremoncillo; Tymiánová nať; Vaistinių čiobrelių žolė; Тимьян Обыкновенный (*Thymus vulgaris*); Ziele tymianku.

ATC Herb — HR05WA5059 (Thymus vulgaris: *herb*); *HA03AW5060* (Thymus vulgaris: *herb*); *HA01WC5007* (Thymus vulgaris: *herb*).

UNII — CW657O8U4N.

NOTE. Distinguish from Wild Thyme, p. 2648.1.

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

Ph. Eur. 8: (Thyme). The whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris*, or *T. zygis*, or a mixture of both species. It contains not less than 12 mL/kg of essential oil, of which a minimum of 40% is thymol and carvacrol, both calculated with reference to the anhydrous drug. It has a strong aromatic odour reminiscent of thymol.

Profile

Thyme is the source of thyme oil (below). It has carminative, antiseptic, antitussive, and expectorant properties and is used chiefly in preparations for respiratory-tract disorders and as a flavour.

General references.

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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Toularynx Thym; *Ger.*: Aspecton; Biotuss†; Bronchipret; Expectysat T; Gelobronchial; Hustagil Thymian-Hustensaft; Hustagil Thymiantropfen; Isephca S†; Melrosum Hustensirup; Nimopect; Pertussin; Soledum Hustensaft; Soledum Hustentropfen; Tetesept Erkaltungs; Thymipin N†; Thymiverlan; Tussamag Hustenlosung†; Tussamag Hustensaft N†; Tussiflorin Thymian; *Hung.*: Hustagil Cough; *Israel*: Thymi Syrup; *Pol.*: Bronchicum N; Bronchicum T; *Rus.*: Bronchicum Husten (Бронхикум Пастилки от Кашля)†; Bronchicum S (Бронхикум С); Tussamag (Туссамаг); *Switz.*: Thymusin N†; *Ukr.*: Bronchostop (Бронхостоп).

Multi-ingredient Preparations. *Arg.*: Cellskinlab Phyto Spot; Expectosan Hierbas y Miel; *Austral.*: Broncafect; Euphorbia Complex†; HRF; *Austria*: Bronchipret; Bronchithym†; Bronchostop; Brust- und Hustentee St Severin; Codelum†; Eicebaer; Hustensaft Weleda; Luuf-Hustentee; Pilka Forte; Pilka; Pneumopan†; Scottopect; Tussamag; Tussimont; *Belg.*: Thymoseptine; *Canad.*: Clear Capsules†; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; *Chile*: Pectokast; Phyto Corrective Gel†; Phyto Spot; Rhus Opodeldoc; Timuss-Kit (sin azucar); Timuss-Kit; *Cz.*: Biotussil; Bronchipret Tymian a Brect'an; Bronchipret Tymian a Prvosenka; Pleumolysin; Pulmoran; Thymomel; Urcyston Planta; *Fin.*: Katapekt; *Fr.*: Biofirm; Depuratum; Dida; Hepato-Solutines†; Mediflor Pectorale d'Alsace no 8†; Pectoflorine†; Santane O1; Saugella Antiseptic; Saugella Antiseptic; Saugella Antiseptic; Saugella Poligyn; Tisane Provencale no 5†; Tussidoron; *Ger.*: Bronchicum Elixir; Bronchicum; Bronchipret; Bronchipret; Broncholitan; Brust- und Hustentee†; Cefabronchin; Cefadrin†; Dr Scheffler Bergischer Krautertee Husten- und Bronchialtee; Drosithym-N†; Ephepect-Pastillen N; Equisil N†; Expectysat N; Kneipp Husten- und Bronchial-Tee†; Makatussin Tropfen; Melissengeist; Phytobronchin; Sinuforton†; Weleda Hustenelixier; *Hung.*: Bronchicum; Bronchicum; Bronchicum; Bronchipret; Bronchipret; Gombarex; Herbalakt; Herpesil; *Indon.* Bronchipret†; Codipront cum Expectorant; Jesscool†; Pectum Silex; Thymcal; *Israel*: Pilka; *Ital.*: Bron 6; Broncosed; Broncosedina; Broncosedina; Enatus; Immumil Plus†; Piodermina; Saugella Attiva; Saugella Fitothym; Saugella Poligyn; Tussol; *Neth.*: Balsoclase Compositum†; Bronchicum; Verzachtende Hoestsiroop met tijm; *Norw.*: Bronchosan†; *Philipp.*: Bronchipret†; *Pol.*: ApiHelix†; Bobodent; Bronchicum Eliksir†; Bronchosol; Dentosept A; Dentosept; Echinasal; Enterosol; Hedelicum; Herbapect; Mucosit; Neoazarina; Pectobonisol; Pectosol; PiniHelix; Salviasept; Saponarex; Septosan†; Tussipect; Tymsal; *Rus.*: Bronchicum (Бронхикум)†; Bronchicum Husten (Бронхикум Сироп от Кашля)†; Bronchicum TP (Бронхикум ТП); Bronchipret (Бронхипрет); Bronchipret TP (Бронхипрет ТП); Codelac Broncho with Thymus Serpyllum (Коделак Бронхо с Чабрецом Обусловлено); Codelac Phyto (Коделак Фито); Eucabal (Эвкабал); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Passifit (Пассифит); Stomatophit (Стоматофит); Stoptussin-Fito (Стоптуссин-фито); *S.Afr.*: Cough Elixir†; *Singapore*: Arkopharma Propolis Spray; Stop Snoring; *Spain*: Pilka; *Swed.*: Alpenkraft; *Switz.*: Bronchipret TP; Bronchosan; DemoPectol; DemoPectol; Elixir contre la toux†; Kernosan 26; Liberol Dragees contre la toux†; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Nican†; Pectoral N; Pilka; Sanotussin; Sirop pectoral; Strath Gouttes contre la toux; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; *Thai.*: Solvopret TP†; Solvopret†; *UK*: Bronchoforce Chesty Cough Ivy Complex; Herb and Honey Cough Elixir; *Ukr.*: Bronchipret (Бронхипрет); Bronchipret TP (Бронхипрет ТП); Bronchostop (Бронхостоп); Bronchostop (Бронхостоп); Eucabal Syrup (Эвкабал Сироп); Herbion Cowslip Syrup (Гербион Сироп Первоцвета); Maraslavin (Мараславин); Pectolvan Phyto (Пектолван Фито); Pectoral (Пекторал); Stomatophyt (Стоматофит); Stomatophyt A (Стоматофит А); Stoptussin Fito (Стоптуссин); Tussavit (Тусавит); *Venez.*: Codebromil; Mixagel; T-Samag.

Homoeopathic Preparations. *Austria*: Tonsan chronisch; *Fr.*: Drosera Complexe No 64; *UK*: Cough Elixir.

Thyme Oil

Esencia de Tomillo; Essência de Tomilho; Kakukkfűolaj; Kekik Yağı; Ol. Thym.; Olejek tymiankowy; Oleum Thymi; Thym, huile essentielle de; Thymi aetheroleum; Thymi Etheroleum; Thymianöl; Timjamiöljy; Timjanolja; Tomillo, aceite esencial de; Tymiánová silice; Vaistinių čiobrelių eterinis aliejus; Тимьяновое Масло.

ATC Herb — HR05WA5058 (Thymus vulgaris: *essential oil*); *HA03AW5059* (Thymus vulgaris: *essential oil*).

UNII — 2UK410MY6B.

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

Ph. Eur. 8: (Thyme Oil, Thymol Type). The essential oil obtained by steam distillation from the fresh flowering aerial parts of *Thymus vulgaris*, *T. zygis*, or a mixture of both species. A clear, yellow or very dark reddish-brown, mobile liquid with an odour reminiscent of thymol. Miscible with dehydrated alcohol and with petroleum spirit. It contains between 36 and 55% of thymol. Store in well-filled, airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Profile

Thyme oil is used similarly to thyme (above). It is also used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Penaten; Thymian Erkaltungs-Bad.

Multi-ingredient Preparations. *Arg.*: Cuassicum; *Austral.*: Olive Leaf Plus; Throat-Clear; *Austria*: Baby Luuf atherische Ole; Bronchostop†; Heumann's Bronchialtee; Luuf-Hustentee; Nasenol; Scottopect; *Belg.*: Perubore†; *Cz.*: Tussilen†; *Fr.*: Balsofumine; Biogaze; Dolirhume; Gouttes aux Essences; Nazinette du Docteur Gilbert; Otylol; Perubore; *Ger.*: Enelbin-Paste†; Erkaltungs Bad N†; Heumann Bronchialtee Solubifix T; Nasulind†; Pulmotin; Retterspitz Innerlich; Schnupfencreme; Tetesept Erkaltungs Bad; Weleda Nasenol; *Gr.*: Ilon; Snufflebabe; *Hung.*: Bronchovit; Carmol; Hustagil Anticold Cream; Pulminetta; *Israel*: Gargol; *Ital.*: Altuss; Calyptol; Fomentil; Naturocil; Valda Timo e Limone; Vegetallumina; *Mon.*: Calyptol; *NZ*: Efalex; Tixylix Chest Rub; *Pol.*: Argol Essenza Balsamica; Argol Grip; Argol Rheuma; Carmolis; Inhalol; Salviasept; *Port.*: Erpecalm; Vaporil; *Rus.*: Carmolis (Кармолис); Carmolis Fluid (Кармолис Жидкость); *S.Afr.*: Balsem Vita GEEL†; Balsem Vita ROOI†; Balsem Vita Wit; Oleum Rhinale Nasal Oil†; Zam-Buk; *Spain*: H Tussan†; Termosan; *Swed.*: Efalex; *Switz.*: Demonatur Capsules contre les refroidissements; DUL-X warm; Echinarom; Eucapinol; Liberol N; Nasmer free; Nasobol Inhalo; Pulmex; Spagyrom; Wala Baume pectoral au plantain; *Thai.*: St Luke's Oil; *Turk.*: Algo-Wax; Mentoseptol; *UK*: Efalex; Nine Rubbing Oils; Snowfire; Snufflebabe; *USA*: Flexall; Maximum Strength Flexall 454; Unguentine.

Homoeopathic Preparations. *UK*: Catarrh Cream.

Thymidine

NSC-21548; Thymine 2-Desoxyriboside; Timidina; Tymidyna; Тимидин.
1-(2-Deoxy-β-D-ribofuranosyl)-5-methyluracil; 1-(2-Deoxy-β-D-ribofuranosyl)-1,2,3,4-tetrahydro-5-methylpyrimidine-2,4-dione.
$C_{10}H_{14}N_2O_5$=242.2
CAS — 50-89-5.
UNII — VC2W18DGKR.

Profile

Thymidine is an endogenous thymine nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). It was formerly given by intravenous infusion to modulate the toxicity of methotrexate but is not considered to be a substitute for calcium folinate; it may also have an antineoplastic action of its own.

Thymidine is given topically with other nucleosides in preparations for the treatment of corneal damage.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Vitacic†; *Mon.*: Vitacic.

Thymus Hormones

Timo, hormonas del.
CAS — 69558-55-0 (thymopentin); 60529-76-2 (thymopoietin); 63340-72-7 (thymic humoral factor).

Profile

The thymus gland controls the development of T-lymphocytes and thereby plays a central role in cell-mediated immunity and the regulation of immune responses. Several polypeptides characterised in the thymus or serum are able to induce lymphocyte differentiation *in vitro* and *in vivo*. They include: thymosin fraction 5, a crude thymus gland extract; thymalfasin (p. 2630.1); thymosin beta 4; thymic humoral factor (THF), isolated from crude thymic extract dialysate; nonathymulin (thymulin, serum thymic factor, Facteur Thymique Serique, FTS), a synthetic nonapeptide; thymomodulin, a partially purified extract from calf thymus; thymogene A, extracted from calf thymus; thymopoietin, a polypeptide of known amino acid sequence; thymopentin (thymopoietin pentapeptide, TP-5), a fragment of thymopoietin with 5 amino acids; and thymostimulin (TP-1), extracted from calf thymus.

Various preparations, including crude extracts from calf thymus gland, thymomodulin, thymopentin, and thymostimulin have been tried as immunomodulators in many conditions including rheumatoid arthritis, diabetes mellitus, immunodeficiency disorders, skin disorders, malignant neoplasms, and some infections.

References.

1. Huff T, *et al.* β-Thymosins, small acidic peptides with multiple functions. *Int J Biochem Cell Biol* 2001; 33: 205–20.
2. Hannappel E, Huff T. The thymosins—prothymosin alpha, parathymosin, and beta-thymosins: structure and function. *Vitam Horm* 2003; 66: 257–96.
3. Goldstein AL, Badamchian M. Thymosins: chemistry and biological properties in health and disease. *Expert Opin Biol Ther* 2004; 4: 559–73.
4. Chen C, *et al.* Roles of thymosins in cancers and other organ systems. *World J Surg* 2005; 29: 264–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Leucotrofina; *Austral.*: Thymunes†; *Braz.*: Leucogen; *China*: An Fa Bu (安法布); HeXin (和信); Ou Ning (歐宁); Qimoxin (奇莫欣); Ti Bo Ding (替波定); Xin Luo Wei (欣洛维); *Ger.*: Thym-Uvocal†; Thymoject†; Thymophysin†; *Pol.*: TFX; *Rus.*: Tactivin (Тактивин); Thymalin (Тималин).

Multi-ingredient Preparations. *Austria*: Wobe-Mugos; *Ger.*: Fega-Coren; NeyDesib Nr 78; *Indon.*: Idesar Plus; *Rus.*: Cytovir (Цитовир).

Homoeopathic Preparations. *Ger.*: AntiFocal Nr 69-Sol L†; Conisan B†; Conjunctisan-BN†; Glandulae-F-Gastreu R20; Hepar comp; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; NeyChon Nr 68; NeyChondrin Nr 68-Sol†; NeyDil Nr 66†; NeyFoc Nr 69; NeyGero Nr 64; NeyGeront Nr 64-Sol L†; NeyGeront Vitalkapsein A; NeyIm Nr 73 pro injectione; NeyImmun Nr 73-Sol†; NeyLing Nr 66; NeyNormin Nr 65; NeySol L 66†; Neythymun†; NeyTroph Nr 96 oral†; NeyTroph Nr 96 pro injectione; NeyTroph Nr96-Sol†; Thymorell; *Neth.*: Emvita 15.

Tiaprost Trometamol *(BANM, rINNM)*

Tiaprost Trometamol; Tiaprostum Trometamolum; Тиапрост Трометамол.
Trometamol salt of (±)-(Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E)-(3RS)-3-hydroxy-4-(3-thienyloxy)but-1-enyl]cyclopentyl}hept-5-enoic acid.
$C_{20}H_{28}O_6S,C_4H_{11}NO_3$=517.6
CAS — 71116-82-0 (tiaprost).

Profile

Tiaprost trometamol is a synthetic analogue of dinoprost (prostaglandin $F_{2\alpha}$). It is used as a luteolytic in veterinary medicine.

Tibezonium Iodide *(rINN)*

Ioduro de tibezonio; Rec-15/0691; Tibezonii Iodidum; Tibezonio, Ioduro de; Tibézonium, Iodure de; Тибезония Йодид.
Diethylmethyl[2-[4-(4-phenylthiophenyl)-3*H*-1,5-benzodiazepin-2-ylthio]ethyl]ammonium iodide.
$C_{28}H_{32}IN_3S_2$=601.6
CAS — 54663-47-7.
ATC — A01AB15.
ATC Vet — QA01AB15.
UNII — E9P274AJEW.

Profile

Tibezonium iodide has been used in the treatment of infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Riposon; *Ital.*: Antoral; *Mex.*: Maxoral†; *Port.*: Maxius.

Tilactase *(rINN)*

EC 3.2.1.23; β-D-Galactosidase; β-Galactosidase; β-D-Galactoside Galactohydrolase; Lactase; Tilactasa; Tilactasum; Тилактаза.
CAS — 9031-11-2.
ATC — A09AA04.
ATC Vet — QA09AA04.

Pharmacopoeias. In *Jpn* (from *Aspergillus oryzae* or *Penicillium multicolor*) and *US* (from *Aspergillus oryzae*).

USP 36: (Lactase). A hydrolytic enzyme derived from *Aspergillus oryzae*. Each g contains not less than 30 000 USP units. Store in airtight containers at room temperature.

Profile

Tilactase hydrolyses lactose into glucose and galactose. It has been added to milk and milk products, or taken orally with a meal containing dairy products, in order to prevent the symptoms of lactose intolerance (p. 2079.1) in persons deficient in the endogenous enzyme.

References.

1. Portincasa P, *et al.* Beneficial effects of oral tilactase on patients with hypolactasia. *Eur J Clin Invest* 2008; 38: 835–44.
2. Ojetti V, *et al.* The effect of oral supplementation with *Lactobacillus reuteri* or tilactase in lactose intolerant patients: randomized trial. *Eur Rev Med Pharmacol Sci* 2010; 14: 163–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lac-Tas; *Canad.*: Dairy Free†; Dairyaid; Lactaid; Lacteeze; LactoMax; Lactrase†; Prolactase; Regular Strength Lactaid; *Chile*: Diolasa; *China*: Lactrase (力德士); *Fr.*: Alvityl Digest; *Ger.*: TilactaMed; *India*: Galazyme-Pro; Lactes; *Irl.*: Colief†; *Ital.*: Lacdigest; Silact; *Jpn*: Galantase; *Mex.*: Enzylac Ultra; *Philipp.*: Lacteeze; *Pol.*: Lactosanol†; *Port.*: Lisolac; *Switz.*: Lacdigest; *Turk.*: Lacdigest; *UK*: Colief; *Ukr.*: Mamalak (Мамалак); *USA*: Dairy Ease; Lac-Dose; Lactaid; Lactrase; SureLac.

Multi-ingredient Preparations. *Austral.*: Vegie Digestaid; *Canad.*: Digesta; Synergy Defense; *Chile*: Lactomol-D; *India*: Leno-EZ; *Ital.*: No Gas Enzimi; *Malaysia*: Lacto Care; *Singapore*: Dairy Care; *USA*: Similase Jr.

Tilarginine *(rINN)*

546C88; BW-546C88; L-NMMA; Targinina; Targinine (BAN); Targininum; Tilarginina; Tilargininum; Таргинин.
N^{ω}-Methyl-L-arginine.
$C_7H_{16}N_4O_2$=188.2
CAS — 17035-90-4.
UNII — 29JT06E6GR.

Profile

Tilarginine is a nitric oxide synthase inhibitor under investigation in the treatment of cardiogenic shock, although results have been disappointing. It has also been tried in septic shock but appears to have been associated with increased mortality. It has also been investigated in migraine.

References.

1. Lassen LH, *et al.* The effect of nitric oxide synthase inhibition on histamine induced headache and arterial dilatation in migraineurs. *Cephalalgia* 2003; 23: 877–86.
2. Bakker J, *et al.* Administration of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; 32: 1–12.
3. Watson D, *et al.* Cardiovascular effects of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) in patients with septic shock: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit Care Med* 2004; 32: 13–20.
4. Lopez A, *et al.* Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; 32: 21–30.
5. Alexander JH, *et al.* TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 2007; 297: 1657–66.
6. Howes LG, Brillante DG. Expert opinion on tilarginine in the treatment of shock. *Expert Opin Invest Drugs* 2008; 17: 1573–80.

Tilia

Hársfavirág; Kwiatostan lipy; Lehmuksenkukka; Liepų žiedai; Lime Flower; Lindblomma; Linden; Lipový květ; Tiliae Flos; Tilleul; Tilleul, fleur de; Tilo; Липовый Цвет.
*ATC Herb — HR05YA5027 (*Tilia cordata*: flower); HN02CW5007 (*Tilia platyphyllos*: flower); HN02CW5006 (*Tilia cordata*: flower); HR05YA5028 (*Tilia platyphyllos*: flower).*
*UNII — CFN6G1F6YK (*Tilia cordata *flower); 1R02M833TN (*Tilia platyphyllos *flower).*

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

Fr. also includes the bark.

Ph. Eur. 8: (Lime Flower). The whole dried inflorescences of *Tilia cordata*, *Tilia platyphyllos*, *Tilia X vulgaris* (=[*Tilia X europaea*]), or a mixture of these species. It has a faint aromatic odour. Protect from light.

Profile

Tilia is mildly astringent and is reputed to have antispasmodic and diaphoretic properties. Lime-flower 'tea' is a traditional domestic remedy.

Various species of tilia are used in herbal preparations for a variety of disorders.

Homoeopathy

Tilia has been used in homoeopathic medicines under the following names: Tilia europaea; Til. euro.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Vibtil; *Cz.*: Lipovy; *Mon.*: Vibtil; *Pol.*: Lipomal.

Multi-ingredient Preparations. *Arg.*: Armonil; Incaico Serenidad; Maprosol Gel; Nervocalm; Phytocalm; Sedanat†; Sedante Dia; Serenil; Valeriana Compuesta; *Austral.*: Aloe Vera Gel; DiaCo; *Austria*: Grippetee St Severin; St Bonifatius-Tee†; *Belg.*: Natudor; *Canad.*: Calmane; Calmane; Detente†; Formula T13 Tea†; Nervinat; Relax Plus; Relaxant; Relaxol; Swiss Herb Cough Drops; *Chile*: Bebe Son; Calmatol; Nature Complex Reduct-Te; Recalm†; Reduc-Te; *Cz.*: Cajova Smes pri Nachlazeni; Pruduskova; *Fr.*: Aromazen†; Azema†; Boribel Tisane No 8†; Lenicalm†; Mediflor Tisane Calmante Troubles du Sommeil No 14; Provencale No 4†; Santane N_6; Tisane Provencale no 4†; Vigilia†; *Israel*: Jungborn†; *Ital.*: Alkagin; Ginepausil; Lenicalm; Saniquiet; Tussol; *Pol.*: Bronchial†; DexaCaps; Fitoven; Melisal; Melissed; Pectobonisol; Pyrosal; Termasil; Tiliros; *Port.*: Alkagin; Alkagin; Alkagin; *Spain*: Agua del Carmen; *Swed.*: Alpenkraft; *Switz.*: Tisane contre les refroidissements; Tisane pour nourissons et enfants; *Turk.*: Alkagin; *UK*: Menopause Relief; Wellwoman; *Ukr.*: Klimased (Климасед).

Homoeopathic Preparations. *Chile*: Melinerv; TBR/X; *Fr.*: Poconeol no 35.

Timonacic *(rINN)*

ATC; NSC-25855; Thioproline; Timonácico; Timonacicum; Тимонацик.
Thiazolidine-4-carboxylic acid.
$C_4H_7NO_2S$=133.2
CAS — 444-27-9.
UNII — E5913T3IBL.

The symbol † denotes a preparation no longer actively marketed

NOTE. The name ATC has also been used for a combination of paracetamol and trichloroethanol (4-acetamidophenyl 2,2,2-trichloroethyl carbonate).

Profile

Timonacic is used as an adjuvant in the treatment of acute and chronic hepatic disorders.

Timonacic methyl hydrochloride (carbolidine hydrochloride) has been used as a mucolytic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Hepacom†; Heparegen.

Tin

Cyna; Estaño; Étain; Stannum; Zinn; Олово.
Sn=118.71
CAS — 7440-31-5.
UNII — 387GMG9FH5 (tin); QI30938BMS (tin ion).

Profile

Tin is a silver-white, lustrous, malleable, ductile metal. Owing to their low solubility, tin and tin oxide are very poorly absorbed from the gastrointestinal tract and have low toxicity. Chronic inhalation causes a benign form of pneumoconiosis.

Organic compounds of tin are highly toxic and may cause liver and kidney damage as well as severe neurological damage associated with oedema of the white matter of the brain. Treatment has been symptomatic. Contamination of the skin with organic tin compounds can cause severe burning; suitable precautions should be taken to prevent absorption of organic tin compounds through the skin.

Tin and tin oxide have been given in the treatment of boils, but there is little evidence of efficacy; they were also formerly used in some countries for the treatment of tapeworm. Organic tin compounds, especially tributyltin oxide (TBTO), are used as molluscicides.

Tin in food. Excess amounts of inorganic tin in food tend to arise from tin-coated cans, especially unlacquered ones, and may produce gastric irritation. Concentrations as low as 150 mg/kg in canned beverages and 250 mg/kg in other canned foods have produced adverse effects in certain individuals, but some foods containing up to 700 mg/kg have not produced any detectable effects. Consumers should be advised not to store foods in opened tinplated cans.[1]

A recommended acceptable daily intake for chronic exposure to tin has been suggested as a provisional tolerable weekly intake of 14 mg/kg, although it was subsequently noted that this value may have been derived from intakes associated with acute effects, and it was concluded that the toxicokinetics and effects of inorganic tin after long-term exposure to dietary doses at concentrations that did not elicit acute effects should be re-assessed.[1] It was also concluded that it was inappropriate to establish an acute reference dose for inorganic tin, since development of gastric irritation depends on the concentration and nature of tin in the food product rather than on the dose ingested on a body-weight basis.[1] In the EU regulations limit the maximum amount of tin in foods sold in member states to wet weights of 200 mg/kg in canned foods other than beverages, 100 mg/kg in canned beverages including fruit and vegetable juices, and 50 mg/kg in various canned foods for infants.[2]

1. FAO/WHO. Evaluation of certain food contaminants: sixty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 930* 2006. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_930_eng.pdf (accessed 22/07/08)
2. The Commission of the European Communities. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Off J EU* 2006; **49:** L364/5–24. Also available at: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_364/l_36420061220en00050024.pdf (accessed 22/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *S.Afr.*: Metinox†.

Homoeopathic Preparations. *Austral.*: Hangover Relief; Respatona Chesty Cough & Nasal Congestion; *Canad.*: Kids Cough & Cold Phytux; Phytotux H; *Fr.*: Abbe Chaupitre no 1†; Kreosotum Complexe No 62; Pulmo-Drainol†; *Ger.*: Derivatio H; Derivatio; Rufebran heparo†; *Hung.*: Klimakt-Heel; *Switz.*: metaossylen N.

Pharmacopoeial Preparations
USP 36: Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets.

Tin-protoporphyrin

Protoporfirina-Estaño; (Sn)-protoporphyrin; Оново-протопорфирин.

Profile

Tin-protoporphyrin and the related compound tin-mesoporphyrin are metalloporphyrins which inhibit haem oxygenase, an enzyme involved in the breakdown of haem to bile pigments. They have been investigated as inhibitors of bilirubin production in hyperbilirubinaemia of various causes, and have been tried in porphyria (p. 1556.1).

References.
1. Valaes T, *et al.* Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. Abstract: *Pediatrics* 1998; **101:** 915. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/5/e1 (accessed 09/07/04)
2. Martinez JC, *et al.* Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics* 1999; **103:** 1–5.
3. Kappas A, *et al.* A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. *Pediatrics* 2001; **108:** 25–30.
4. Kappas A, *et al.* Sn-mesoporphyrin interdiction of severe hyperbilirubinemia in Jehovah's Witness newborns as an alternative to exchange transfusion. *Pediatrics* 2001; **108:** 1374–7.
5. Kappas A. A method for interdicting the development of severe jaundice in newborns by inhibiting the production of bilirubin. *Pediatrics* 2004; **113:** 119–23.
6. Drummond GS, Kappas A. Chemoprevention of severe neonatal hyperbilirubinemia. *Semin Perinatol* 2004; **28:** 365–8.
7. Dennery PA. Metalloporphyrins for the treatment of neonatal jaundice. *Curr Opin Pediatr* 2005; **17:** 167–9.

Tiropramide Hydrochloride *(rINN)*

Hidrocloruro de tiropramida; Tiropramida, hidrocloruro de; Tiropramide, Chlorhydrate de; Tiropramidi Hydrochloridum; Тиропрамида Гидрохлорид.
α,-α-Benzamido-*p*-[2-(diethylamino)ethoxy]-*N,N*-dipropylhydrocinnamamide hydrochloride.
$C_{28}H_{41}N_3O_3,HCl$=504.1
CAS — 55837-29-1 (tiropramide); 57227-16-4 (tiropramide hydrochloride).
ATC — A03AC05.
ATC Vet — QA03AC05.
UNII — 9523013Y6R.

Profile

Tiropramide hydrochloride is used as an antispasmodic. Doses of 100 mg 2 or 3 times daily or 200 mg twice daily have been given orally. It has also been given rectally and parenterally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Alfospas; Maiorad†; *Philipp.*: Triopan; *Port.*: Maiorad; *Thai.*: Maiorad.

Titanium

Titan; Titane; Titanio; Tytan; Титан.
Ti=47.867
CAS — 7440-32-6.
UNII — D1JT611TNE.

Profile

Titanium has been used in the repair of skull damage and for implantation in dental surgery.

References.
1. Brown D. All you wanted to know about titanium, but were afraid to ask. *Br Dent J* 1997; **182:** 393–4.
2. Williams D. The golden anniversary of titanium biomaterials. *Med Device Technol* 2001; **12:** 8–11.
3. Sicilia A, *et al.* Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res* 2008; **19:** 823–35.
4. Ohkubo C, *et al.* Present status of titanium removable dentures—a review of the literature. *J Oral Rehabil* 2008; **35:** 706–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Minesol.

Tobacco

Cultivated Tobacco; Nicotiane; Tabac; Tabac Commun; Tabaco; Tabacum; Tabak; Tobak; Virginiantupakka; Virginiatobak; Virginischer Tabak; Virginsk Tobak; Yan Cao; Табак; Тютюн.
UNII — 6DI1HBV20R (Nicotiana tabacum); 6YR2608RSU (Nicotiana tabacum leaf).

Profile

Tobacco is the prepared and cured leaves of *Nicotiana tabacum* (Solanaceae) and related species. Tobacco was formerly used medicinally, but now is most commonly used as a recreational drug, typically by smoking, chewing, or as snuff. Although tar and other products of combustion contribute to the adverse effects of smoking, the physiological and addictive properties of tobacco products derive from the content of the alkaloid nicotine; for discussion of the effects of tobacco use, see under Nicotine, p. 2569.3.

Homoeopathy

Tobacco is also used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Smoke Eze; Traveller Relief; *Austria*: Katerex; Travelex; *Canad.*: Ateria-Heel†; Cocculine; Formula TA 220†; Homeo-Form T†; Hylands Motion Sickness; Nixotinex; *Cz.*: Cocculine; *Fr.*: Cocculine; Dolitravel†; Homeogene 21†; Nausetum; Tabacum Compose; Tabapass; *Ger.*: Aconitum Nicotiana comp†; Arte-cyl Ho-Len-Complex; metabiarex; metaginkgo†; Otio-cyl Ho-Len-Complex; Oto-cyl Ho-Len-Complex; Procordal vertigo; Tabarell; Vasa-Gastreu N R63; Vertigo Hevert SL; *Hung.*: Cocculine; *Neth.*: Cocculine; Gletar; Gravifem†; Travelin; *Port.*: Cocculine; *Rus.*: Cocculine (Коккулин); Tabacum-Plus (Табакум-Плюс); Tonginal (Тонгинал); *Switz.*: Cocculine; metaginkgo; Nelsons Travella†; *UK*: Travella; *Ukr.*: Tonginal (Тонгинал).

Tolonium Chloride *(rINN)*

CI Basic Blue 17; Cloruro de tolonio; Colour Index No. 52040; Tolonii Chloridum; Tolonio, cloruro de; Tolonium, Chlorure de; Toluidine Blue O; Толония Хлорид.
3-Amino-7-dimethylamino-2-methylphenazathionium chloride.
$C_{15}H_{16}ClN_3S$=305.8
CAS — 92-31-9.
UNII — 15XUH0X66N.

NOTE. Distinguish from Toluidine Blue, Colour Index No. 63340.

Profile

Tolonium chloride is a thiazine dye chemically related to methylthioninium chloride (p. 1559.1). It has been used to stain oral and gastric neoplasms and was given intravenously to stain the parathyroid glands. Other uses have included the treatment of menstrual disorders and methaemoglobinaemia.

Tolonium chloride should be avoided in patients with G6PD deficiency as haemolysis may occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Toluidinblau; *Ger.*: Toluidinblau; *Gr.*: Orascreen; OraTest; *Neth.*: OraTest†; *NZ*: Orascreen; *Port.*: OraTest.

Tolvaptan *(BAN, USAN, rINN)* ⊗

OPC-41061; Tolvaptán; Tolvaptanum; Толваптан.
(±)-4′-[(7-Chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl)carbonyl]-o-tolu-*m*-toluidide.
$C_{26}H_{25}ClN_2O_3$=448.9
CAS — 150683-30-0.
ATC — C03XA01.
ATC Vet — QC03XA01.
UNII — 21G72T1950.

Uses and Administration

Tolvaptan is a selective vasopressin V_2-receptor antagonist used to treat euvolaemic and hypervolaemic hyponatraemia (p. 1778.1) including that in heart failure and syndrome of inappropriate antidiuretic hormone secretion. Tolvaptan therapy should be started in hospital.

Tolvaptan is given orally in a single daily dose of 15 mg, which may be increased after at least 24 hours to 30 mg. The dose should be adjusted up to a maximum of 60 mg once daily to achieve the desired serum-sodium concentrations. US licensed product information recommends that treatment should be continued for no longer than 30 days (see Adverse Effects and Precautions, p. 2633.1). Patients should be monitored for changes in serum electrolytes and volume during the initiation and titration phase especially those at high risk of demyelination syndromes such as patients with hypoxia, alcoholism, malnutrition, or a very low serum sodium at baseline. Fluid restriction should be avoided during the first 24 hours of therapy, and patients should be instructed to drink fluids in response to thirst. If a rapid rise in serum-sodium occurs (more than 12 mmol/litre

in 24 hours) tolvaptan should be stopped, and serum-sodium and neurological status should be carefully monitored because of the risk of osmotic demyelination syndrome; hypotonic fluid should be considered in patients whose serum-sodium rises too rapidly. If hypovolaemia develops, tolvaptan therapy should be interrupted or stopped and volume status and vital signs monitored with supportive care as required. At the end of tolvaptan therapy, patients should resume fluid restriction and be monitored for changes in serum-sodium and volume status.

Adjustment of tolvaptan doses or monitoring of potassium concentrations may be required when tolvaptan is given with some other drugs—see Interactions below.

References.
1. Plosker GL. Tolvaptan. *Drugs* 2010; 70: 443–54.
2. Cyr PL, *et al.* Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. *Am J Health-Syst Pharm* 2011; 68: 328–33.
3. Amin A, Meeran K. New drugs for hyponatraemia: evidence is lacking that they are better than cheaper standard treatment. *BMJ* 2011; 342: 559–60.
4. Peri A. The use of vaptans in clinical endocrinology. *J Clin Endocrinol Metab* 2013; 98: 1321–32.

Cystinuria. Tolvaptan 15 mg orally, once daily for 5 days substantially increased urine output in 2 patients with homozygous cystinuria.[1] This resulted in urinary cystine concentrations below the level at which cystine stone formation could occur, suggesting that tolvaptan may be useful to prevent formation of new stones and help to dissolve existing ones.

1. de Boer H, *et al.* Antidiuretic hormone antagonist to reduce cystine stone formation. *Ann Intern Med* 2012; 157: 459–60.

Polycystic kidney disease. In a study in patients with autosomal dominant polycystic kidney disease treatment with tolvaptan slowed the rate of increase in kidney volume and the decline in renal function compared with placebo over a 3-year period.[1]

1. Torres VE, *et al.* TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–18.

Adverse Effects and Precautions

The most common adverse effects of tolvaptan are thirst, dry mouth, asthenia, nausea, constipation, hyperglycaemia, and pollakiuria or polyuria. Water loss may be excessive and dehydration and hypovolaemia can occur.

Tolvaptan is contra-indicated in hypovolaemic hyponatraemia, in patients who require a rapid increase in serum-sodium concentrations, and in those who cannot sense or who respond inappropriately to thirst. Rapid correction of serum-sodium concentrations with tolvaptan could increase the risk of osmotic demyelination syndrome. Tolvaptan is ineffective and therefore inappropriate to use in anuric patients. Tolvaptan can cause serious and potentially fatal liver injury and it should be stopped if symptoms suggesting liver injury occur. *US licensed product* information recommends that treatment with tolvaptan is limited to a maximum of 30 days to reduce the risk of liver injury; it also states that tolvaptan should be avoided in patients with underlying liver disease including cirrhosis.

Interactions

As a substrate of the cytochrome P450 isoenzyme CYP3A4, concentrations of tolvaptan can be increased by CYP3A4 inhibitors. The use of tolvaptan with potent CYP3A4 inhibitors such as clarithromycin, ketoconazole, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin is contra-indicated. Use of tolvaptan with moderate CYP3A4 inhibitors such as aprepitant, diltiazem, erythromycin, fluconazole, and verapamil should also be avoided on theoretical grounds that an increase in tolvaptan concentrations would also be expected.

Rifampicin is a CYP3A4 inducer and significantly reduces tolvaptan concentrations. It is expected that other CYP3A4 inducers such as rifabutin, rifapentine, barbiturates, carbamazepine, phenytoin, and St John's Wort would have the same effect. Therefore concomitant use of tolvaptan with CYP3A4 inducers should be avoided where possible.

Ciclosporin or grapefruit juice may increase tolvaptan concentrations.

For the effect of tolvaptan on digoxin, see p. 1358.1.

Hyperkalaemia has been reported in patients taking tolvaptan at the same time as angiotensin II receptor antagonists, ACE inhibitors, or potassium sparing diuretics. Monitoring of potassium concentrations is recommended when any of these drugs are given with tolvaptan.

Pharmacokinetics

Peak concentrations of tolvaptan occur about 2 to 4 hours after oral doses. It is metabolised mainly, if not exclusively, by the cytochrome P450 isoenzyme CYP3A4, and is highly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Samsca; *Cz.*: Samsca; *Denm.*: Samsca; *Ger.*: Samsca; *Irl.*: Samsca; *Jpn*: Samsca; *Neth.*: Samsca; *Norw.*: Samsca; *Pol.*: Samsca; *Port.*: Samsca; *Spain*: Samsca; *Swed.*: Samsca; *UK*: Samsca; *USA*: Samsca.

Tormentil

Blodrot; Consolda Vermelha; Consuelda roja; Erect Cinquefoil; Miškinių sidabražolių šakniastiebiai; Nátržníkový oddenek; Rätvänänjuurakko; Sietenrama; Tormentilla; Tormentillae rhizoma; Tormentille; Tormentillwurzelstock; Vérontófűgyökértörzs; Калган (*Potentilla erecta*); Лапчатка Прямостоячая (*Potentilla erecta*).

UNII — B1896CKT6B.

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

Ph. Eur. 8: (Tormentil). The whole or cut, dried rhizome, freed from the roots, of *Potentilla erecta* (*P. tormentilla*). It contains not less than 7% of tannins expressed as pyrogallol, calculated with reference to the dried drug. Protect from light.

Profile

Tormentil has astringent properties and is used in herbal preparations for diarrhoea and other indications. Gastro-intestinal irritation and vomiting have occasionally occurred.

References.
1. Subbotina MD, *et al.* Effect of oral administration of tormentil root extract (Potentilla tormentilla) on rotavirus diarrhea in children: a randomized, double blind, controlled trial. *Pediatr Infect Dis J* 2003; 22: 706–11.
2. Huber R, *et al.* Tormentil for active ulcerative colitis: an open-label, dose-escalating study. *J Clin Gastroenterol* 2007; 41: 834–8.
3. Tomczyk M, Latté KP. Potentilla—a review of its phytochemical and pharmacological profile. *J Ethnopharmacol* 2009; 122: 184–204.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Tormentasan†.

Multi-ingredient Preparations. *Cz.*: Dr Theiss Schwedenbitter†; Herbadent; Original Schwedenbitter; Tormentan; *Ger.*: Repha-Os†; *Hung.*: Bano Svedkeseru; Travelon; *Pol.*: Hemorol; Neo-Tormentil; Stomatosol; Tobacoff; Tormentile Forte; Tormentiol; *Rus.*: Fitantis (Фитантис); Linkus (Линкас); Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); *Switz.*: Baume Zeller; Pommade au Baume; *Ukr.*: Linkus (Линкас); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†.

Homoeopathic Preparations. *Switz.*: Diarrheel S.

Pharmacopoeial Preparations
Ph. Eur.: Tormentil Tincture.

Transfer Factor

Transferencia, factor de; Трансферный Фактор.

Profile

Transfer factor is a peptide constituent of dialysable leucocyte extracts prepared from the leucocytes of a sensitised donor, that can passively transfer cell-mediated immunity to a non-sensitised recipient.

Transfer factor has been suggested for use in infections due to bacteria, fungi, and viruses, inflammatory disorders, skin disorders such as eczema, nervous system disorders, immunodeficiency diseases, and malignancies, although the response when it has been tried in some of these conditions has not always been satisfactory.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Gan Sheng Su (肝生素); JinGanTai (金甘泰); Oligotide (臭肝肽); Tai Lai Tai (泰来肽); YiKangNing (亿康宁); *Cz.*: Imunor.

Transforming Growth Factor Antibodies

Антитела к Трансформирующему Фактору Роста.

Profile

A human monoclonal antibody specific for transforming growth factor β1 is under investigation for the treatment of systemic sclerosis.

Lerdelimumab (p. 2544.1) is a human monoclonal antibody specific for transforming growth factor β2.

Trepibutone *(rINN)*

AA-149; Trepibutona; Trépibutone; Trepibutonum; Trepionate; Трепибутон.

3-(2,4,5-Triethoxybenzoyl)propionic acid.

$C_{16}H_{22}O_6$=310.3

CAS — 41826-92-0.

ATC — A03AX09.

ATC Vet — QA03AX09.

UNII — H1187LU49Q.

Pharmacopoeias. In *Jpn.*

Profile

Trepibutone has been reported to have spasmolytic and choleretic activity and has been used in biliary-tract disorders and pancreatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Port.*: Choliatron.

Tribenoside *(BAN, USAN, rINN)*

21401-Ba; Ba-21401; Tribenosid; Tribénoside; Tribenosidi; Tribenósido; Tribenosidum; Tribenozid; Tribenozidas; Трибенозид.

Ethyl 3,5,6-tri-O-benzyl-D-glucofuranoside.

$C_{29}H_{34}O_6$=478.6

CAS — 10310-32-4.

ATC — C05AX05; C05CX01.

ATC Vet — QC05AX05; QC05CX01.

UNII — Z7N0Y673NU.

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

Ph. Eur. 8: (Tribenoside). A yellowish to pale yellow, clear, viscous liquid. Practically insoluble in water; very soluble in acetone, in dichloromethane, and in methyl alcohol. Store under nitrogen in airtight containers.

Profile

Tribenoside has been used in inflammatory and varicose disorders of the veins, including haemorrhoids (p. 1808.1). It has been given orally in usual doses of 800 mg daily. It has also been given rectally and topically.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Glyvenol; *Cz.*: Glyvenol; *Gr.*: Glyvenol; *Mex.*: Glyvenol; *Philipp.*: Glyvenol; *Rus.*: Glyvenol (Гливенол); *Venez.*: Glyvenol.

Multi-ingredient Preparations. *Arg.*: Procto-Glyvenol; *Braz.*: Procto-Glyvenol; *Chile*: Euproct; Procto-Glyvenol; Proctogel; *Cz.*: Procto-Glyvenol; *Gr.*: Procto-Glyvenol; *Israel*: Procto-Glyvenol; *Mex.*: Procto-Glyvenol; *Philipp.*: Procto-Glyvenol; *Pol.*: Procto-Glyvenol; Procto-Hemolan; Venozel; *Port.*: Procto-Glyvenol; *Rus.*: Procto-Glyvenol (Прокто-Гливенол); *Switz.*: Procto-Glyvenol; *Turk.*: Procto-Glyvenol; *UAE*: Haemoproct; *Ukr.*: Procto-Glyvenol (Прокто-Гливенол); *Venez.*: Bargonil; Procto-Glyvenol.

Tribulus Terrestris ⊗

Caltrp.; Gokhru; Jili; Puncture Vine; Puncturevine; Tribulus; Якорцы Стелющиеся (*Tribulus terrestris*).

UNII — 4X4HLN92OT (Tribulus terrestris); *8JMX062MNR (Tribulus terrestris flower); QNL076V6EQ (Tribulus terrestris fruit); 6WY8ROM74K* (Tribulus terrestris *root).*

Pharmacopoeias. In *Chin.* and *Jpn*, which specify the fruit.

Profile

The fruit, flowers, and root of *Tribulus terrestris* (Zygophyllaceae) are used in herbal medicine for many different purposes, including the treatment of urinary stones and other urinary disorders, for digestive disorders, for male sexual disorders, and as a diuretic and an aphrodisiac.

The fruit is also used in Ayurvedic and traditional Chinese medicine.

It is included in dietary supplements and tonics, and has been taken by athletes for its reported anabolic effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Androsten; *Indon.*: Tribestan; *Rus.*: Tribestan (Трибестан); *Singapore*: Tribestan; *Ukr.*: Tribestan (Трибестан).

Multi-ingredient Preparations. *Austral.*: Enhance for Men; Femi-Nan; Mens Performance Multi; The Blue One†; Tribulus & Epi-

medium Compound; *Canad.*: Libeeda for Men; Libeeda for Women; *Hung.*: Munipyrin; *India*: Addyzoa; Alka; Benprost-B; Bonnisan; Calcury; Confido; Cystone; Diabecon; Distone; Femi Forte; Femiplex; Flush; Flush; Galakol; Geriforte; Gynodex; Gynoset; Himplasia; Kof-Rid; Lactare; Laforte; Manix; Manoll; Mustong; Neeri; Nefid; Pallrywyn Forte; *Indon.*: Bioretin†; Instink†; Maxirex; Reximax; Sirec; Tetris; Tristan†; *Ital.*: Cistefi; *Jpn*: Tokiinshi; *Malaysia*: Bonnisan; Rumalaya; *Philipp.*: Cogent db+; *Rus.*: Fitovit (Фитовит); Speman (Спеман); Speman Forte (Спеман Форте); Verona (Верона); *Singapore*: Andromet; Cystone; Tentex Royal; *Ukr.*: Andropower (Андропауэр); Bon-Apetit (Бон-Аппетит); Confido (Конфидо)†; Fitovit (Фитовит); Imunin (Иммунин)†; Speman (Спеман); Verona (Верона).

Trichophyton Antigen

Trichophytin.

Profile

Preparations containing antigens extracted from *Trichophyton* spp. (a cause of fungal skin infections) have been used to assess cell-mediated immunity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Multitest CMI†; *Gr.*: Multitest.

Trilostane *(BAN, USAN, pINN)*

Trilostaani; Trilostan; Trilostano; Trilostanum; Win-24540; Трилостан.

4α,5α-Epoxy-17β-hydroxy-3-oxoandrostane-2α-carbonitrile.

$C_{20}H_{27}NO_3$=329.4

CAS — 13647-35-3.

ATC — H02CA01.

ATC Vet — QH02CA01.

UNII — L0FPV48Q5R.

Uses and Administration

Trilostane is an adrenocortical suppressant that inhibits the enzyme system essential for the production of glucocorticoids and mineralocorticoids. It is used for the treatment of adrenal cortical hyperfunction such as Cushing's syndrome and primary hyperaldosteronism. It is also used in postmenopausal breast cancer that has relapsed after oestrogen antagonist therapy.

The usual daily dose in adrenal cortical hyperfunction is 240 mg orally in divided doses for at least 3 days and then adjusted, according to response, within the range of 120 to 480 mg daily. Doses of 960 mg daily have been given.

In postmenopausal breast cancer an initial daily dose of 240 mg is given orally in divided doses, with glucocorticoid replacement therapy. This is increased in steps of 240 mg every 3 days up to a maintenance dose of 960 mg daily; this may be reduced to 720 mg daily if adverse effects are intolerable.

Adverse Effects

Adverse effects associated with trilostane have included flushing, nausea, vomiting, diarrhoea, rhinorrhoea, and tingling and swelling of the mouth. Rashes may occur and, rarely, granulocytopenia in immunocompromised patients.

Precautions

Trilostane is contra-indicated in pregnancy and should be used with caution in patients with renal or hepatic impairment. Circulating corticosteroids and blood electrolytes should be monitored. In some patients, supplementation with corticosteroids may be necessary.

Interactions

Trilostane may interfere with the activity of oral contraceptives. Hyperkalaemia may occur if trilostane is given with potassium-sparing diuretics or aldosterone antagonists.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Desopan; *UK*: Modrenal†.

Trimebutine Maleate *(BANM, rINNM)*

Maleato de trimebutina; Trimebutin Maleat; Trimebutina, maleato de; Trimébutine, maléate de; Trimebutini Maleas; Тримебутина Малеат.

2-Dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoate hydrogen maleate.

$C_{22}H_{29}NO_5.C_4H_4O_4$=503.5

CAS — 39133-31-8 (trimebutine); 34140-59-5 (trimebutine maleate).

ATC — A03AA05.

ATC Vet — QA03AA05.

UNII — 2A051GM4YM.

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

Ph. Eur. 8: (Trimebutine Maleate). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in acetone; soluble in acetonitrile.

Profile

Trimebutine maleate has been used as an antispasmodic in gastrointestinal disorders in oral doses of up to 600 mg daily in divided doses. It has also been given by injection and rectally. Trimebutine base has also been used.

Irritable bowel syndrome. Trimebutine has been reported[1-3] to be effective in the treatment of irritable bowel syndrome (p. 1810.3) although a considerable placebo response has been seen.[1] Its action is thought to be mediated both via gastrointestinal opioid receptors and modulation of the release of gastrointestinal peptides.[4]

1. Ghidini O, *et al.* Single drug treatment for irritable colon: rociverine versus trimebutine maleate. *Curr Ther Res* 1986; 39: 541–8.
2. Schaffstein W, *et al.* Comparative safety and efficacy of trimebutine versus mebeverine in the treatment of irritable bowel syndrome. *Curr Ther Res* 1990; 47: 136–45.
3. Kountouras J, *et al.* Efficacy of trimebutine therapy in patients with gastroesophageal reflux disease and irritable bowel syndrome. *Hepatogastroenterology* 2002; 49: 193–7.
4. Delvaux M, Wingate D. Trimebutine: mechanism of action, effects on gastrointestinal function and clinical results. *J Int Med Res* 1997; 25: 225–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Altrip; Biorgan; Colixane; Debridat; Eumotil; Fenatrop; Miopropan; Plidex T; Plidex; Tributina†; *Braz.*: Digedrat; *Canad.*: Modulon; *Chile*: Debridat; Dolpic Forte; Tidomel; Trim; *China*: Cerekinon (舒丽启能); Diway (诺为); Ni Wei Fu (尼为孚); Rui Jian (瑞健); Shuang Di (双迪); Yuan Sheng Li Wei (援生力维); *Fr.*: Debricalm; Debridat; Modulon†; Transacalm; *Gr.*: Garapepsin; Ibutin; Trienter; *Hong Kong*: Cerekinon; *Ital.*: Debridat; Digerent; *Jpn*: Cerekinon; *Malaysia*: Cerekinon; Trima†; *Mex.*: Cineprac; Crismotil; Debridat; Dolbutin; Espabion; Farbutin†; Krisxon; Libertrim; Muttifen; Prescol; Scitin; *Pol.*: Debretin; Debridat; Tribux; *Port.*: Debridat; *Rus.*: Trimedat (Тримедат); *Singapore*: Cerekinon; Debridat; *Spain*: Polibutin; *Switz.*: Debridat; *Thai.*: Cerekinon; *Turk.*: Debridat; Gismotal; Tribudat; *Ukr.*: Tribudat (Трибудат); *Venez.*: Bumetin; Colypan.

Multi-ingredient Preparations. *Arg.*: Biorgan B; Colixane B; Debridat B; Eumotil-T; Fenatrop-A†; Miopropan Proctologico; Miopropan S; Miopropan-T; *Fr.*: Proctolog; *Gr.*: Ibuproct; *Ital.*: Debrum; *Mex.*: Libertrim SDP; Libertrim SII; *Port.*: Proctolog; *Singapore*: Proctolog; *Spain*: Proctolog; *Turk.*: Proctolog; Progtolog.

Trinitrophenol

Ácido pícrico; Carbazotic Acid; Kwas pikrynowy; Picric Acid; Picrinic Acid; TNP; Trinitrofenol; Тринитрофенол.

2,4,6-Trinitrophenol.

$C_6H_3N_3O_7$=229.1

CAS — 88-89-1.

UNII — A49OS0F91S.

Pharmacopoeias. In *Fr.*

Storage and hazards. Trinitrophenol burns readily and explodes when heated rapidly or when subjected to percussion.

For safety in handling, trinitrophenol is usually supplied mixed with not less than half its weight of water. It should be stored in a cool place. It must not be stored in glass-stoppered bottles.

Trinitrophenol combines with metals to form salts, some of which are very explosive.

Profile

Trinitrophenol has disinfectant properties and was formerly used in the treatment of burns. It is now chiefly used in manufacturing and as a laboratory reagent.

Dermatitis, skin eruptions, severe itching, and yellow staining of the skin may occur after contact with trinitrophenol. Systemic toxicity may follow ingestion or absorption through the skin or lungs; symptoms may include vomiting, pain, and diarrhoea, progressing to haemolysis, hepatitis, anuria, convulsions, unconsciousness, and death. The metabolic rate is increased, causing pyrexia.

Homoeopathy

Trinitrophenol and its salts have been used in homoeopathic medicines under the following names:

- Trinitrophenol: Picricum acidum; Picricum ac
- Calcium picrate: Calcarea picrata; Cal. pic.; Calc pic.
- Iron picrate: Ferri picras; Ferric picrate; Ferrum picricum; Ferr-pic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Agua Sulfatada Picrica† *Spain*: Oftalmol Ocular.

Homoeopathic Preparations. *Austral.*: Hangover Relief; Vitaton Energy†; *Austria*: Acidum picrinicum Med Complex†; Asarum Med Complex; Erbiode Akne; Gentos; Phosphorus Med Complex; Valerianaheel; *Canad.*: Acne; Homeo-Form M†; Menta Alertness; Valerianaheel Comp†; *Fr.*: Acidum Phosphoricum Complexe No 5; Sabal Serrulata Compose; *Ger.*: Evisco Mistel tropfen N; Neuro-Ginsan N; Presselin Nervenkomplex; Presselin Nervennahrung N†; Prostata-Gastreu N R25; Prostata-Komplex L Ho-Fu-Complex; Prostata-Komplex N Ho-Fu-Complex† Sedacalman; Viragil; *Hung.*: Gentos; *Rus.*: Gentos (Гентос) *Ukr.*: Gentos (Гентос); *USA*: Preferred Remedies Fatigue.

Trolamine *(pINN)*

TEA; Trietanolamina; Trietanoloamina; Triethanolamine; Trolamiini; Trolamin; Trolamina; Trolaminas; Trolaminum; Троламин.

CAS — 102-71-6.

UNII — 9O3K93S3TK.

Description. Trolamine is a variable mixture of bases containing mainly 2,2′,2″-nitrilotriethanol (trolamine $(CH_2OH.CH_2)_3N$), with 2,2′-iminobisethanol (diolamine) and smaller amounts of 2-aminoethanol (monoethanolamine).

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

Ph. Eur. 8: (Trolamine; Triethanolamine BP 2014). A clear, viscous, colourless or slightly yellow, very hygroscopic liquid. Miscible with water and with alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Trolamine). A mixture of alkanolamines consisting largely of trolamine containing some diolamine and monoethanolamine. A colourless to pale yellow, viscous, hygroscopic liquid having a slight ammoniacal odour. Miscible with water and with alcohol; soluble in chloroform. Store in airtight containers. Protect from light.

Uses and Administration

Trolamine is used with fatty acids such as stearic and oleic acids as an emulsifier and as an alkalinising agent. It has also been used to reduce dithranol-induced staining of the skin.

Ear drops containing trolamine polypeptide oleate-condensate 10% are used for the removal of impacted ear wax (p. 1836.3).

Trolamine salicylate (p. 141.2) has also been used.

Reviews.

1. Del Rosso JQ, Bikowski J. Trolamine-containing topical emulsion: clinical applications in dermatology. *Cutis* 2008; 81: 209–14.

Radiotherapy. An emulsion of trolamine has been widely used in the treatment and prevention of radiation-induced dermatitis in patients undergoing radiotherapy. However, several studies have suggested that it is of little or no benefit.[1-3]

1. Fisher J, *et al.* Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys* 2000; 48: 1307–10.
2. Szumacher E, *et al.* Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys* 2001; 51: 81–6.
3. Elliott EA, *et al.* Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *J Clin Oncol* 2006; 24: 2092–7.

Adverse Effects

Trolamine salts may be irritating to the skin and mucous membranes. Contact dermatitis has been reported after the use of ear drops containing trolamine polypeptide oleate-condensate.

Carcinogenicity. Because of concern about the possible production of carcinogenic nitrosamines in the stomach, the Swiss authorities restricted the use of trolamine to preparations for external use.[1]

1. Anonymous. Trolamine: concerns regarding potential carcinogenicity. *WHO Drug Inf* 1991; 5: 9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biafine; Reumosan Flex; Solucer; *Belg.*: Lamiderm; Xerumenex; *Canad.*: Cerumenex†; *Chile*: Biafine; *China*: Biafine (比亚芬); *Fr.*: Biafine; Biafineact; Lamiderm; *Ger.*: Cerumenex N; *Israel*: Biafine; *Mex.*: Orlawax; *Port.*: Biafine; *Singapore*: Biafine; *Switz.*: Biafine; Cerumenex; *USA*: Biafine; *Venez.*: Biafine.

Multi-ingredient Preparations. *Arg.*: Tereonsit; *Braz.*: Cerumin; Paraqueimol; *Canad.*: Soropon†; *Ital.*: Dopo Pik; *Turk.*: Sac-Bi-Toks; *USA*: Maxilube; Neosalus; Sonafine.

Trometamol *(BAN, rINN)* ⊗

NSC-6365; THAM; Trihydroxymethylaminomethane; TRIS; Tris (hydroksymetylo)aminometan; Tris(hydroxymethyl)aminomethane; Trometamina; Trometamol; Trometamolis; Trometamolum; Tromethamine (USAN); Трометамол.

2-Amino-2-(hydroxymethyl)propane-1,3-diol.

$C_4H_{11}NO_3$=121.1.

CAS — 77-86-1.

ATC — B05BB03; B05XX02.

ATC Vet — QB05BB03; QB05XX02.

UNII — 023C2WHX2V.

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

Ph. Eur. 8: (Trometamol). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ethyl acetate. A 5% solution in water has a pH of 10.0 to 11.5.

USP 36: (Tromethamine). A white, crystalline powder having a slight characteristic odour. Soluble 1 in 1.8 of water and 1 in 45.5 of alcohol; freely soluble in low-molecular-weight aliphatic alcohols; practically insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 5% solution in water is between 10.0 and 11.5. Store in airtight containers.

Incompatibility. There is evidence to suggest that fluorouracil degrades to cardiotoxic compounds in formulations buffered with trometamol.[1]

1. Lukaschek J, *et al.* Cardiotoxicity and neurotoxicity of high-dose continuous fluorouracil as a result of degradation compounds in the drug vials. *J Clin Oncol* 2004; **22:** 5022–5.

Uses and Administration

Trometamol is an organic amine proton acceptor used as an alkalinising agent in the treatment of metabolic acidosis (p. 1775.2). It also acts as a weak osmotic diuretic. Trometamol is mainly used during cardiac bypass surgery and during cardiac arrest. It may also be used to reduce the acidity of citrated blood for use in bypass surgery.

The dose used should be the minimum required to increase the pH of the blood to within normal limits and is based on the body-weight and the base deficit. Trometamol is given by slow intravenous infusion as a 0.3M solution; it should not be given for longer than a day except in life-threatening emergencies.

Trometamol citrate is given orally for the management of urinary calculi and acidosis. Trometamol acefyllinate has also been used for acidosis.

References.

1. Nahas GG, *et al.* Guidelines for the treatment of acidaemia with THAM. *Drugs* 1998; **55:** 191–224.

Adverse Effects and Precautions

Great care must be taken to avoid extravasation at the injection site as solutions may cause tissue damage. Local irritation, venospasm and phlebitis have occurred.

Respiratory depression can occur and mechanical ventilation may be required. Hypoglycaemia may also occur. Trometamol is contra-indicated in anuria and uraemia, and should be used cautiously in patients with renal impairment as hyperkalaemia has been reported in such patients. Trometamol is not recommended for use in patients with respiratory acidosis alone. If it is used in patients with respiratory acidosis accompanying metabolic acidosis, ventilation should be maintained mechanically. Trometamol is contra-indicated in chronic respiratory acidosis.

Blood concentrations of bicarbonate, glucose, and electrolytes, partial pressure of carbon dioxide, and blood pH should be monitored during infusion of trometamol.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trometamol 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 06/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Tham†; *Canad.*: Tham; *Ger.*: Tham; Tris; *Gr.*: Tham; *Ital.*: Thamesol; *Singapore*: Tham; *Swed.*: Addex-THAM.

Multi-ingredient Preparations. *Austral.*: Blink-N-Clean; *Fr.*: Alcaphor; *Malaysia*: Cationorm; *Norw.*: Tribonat; *Spain*: Cardi-Braun; *Swed.*: Tribonat.

Pharmacopoeial Preparations

USP 36: Tromethamine for Injection.

Trypan Blue

CI Direct Blue 14; Colour Index No. 23850; Trypanum Caeruleum; Трипановый Синий.

Tetrasodium 3,3′-[(3,3′-dimethylbiphenyl-4,4′-diyl)bisazo]bis [5-amino-4-hydroxynaphthalene-2,7-disulphonate].

$C_{34}H_{24}N_6Na_4O_{14}S_4$=960.8

CAS — 72-57-1.

UNII — I2ZWO3LS3M.

Profile

Trypan blue solutions are used as stains in microscopy and for visualisation of various tissues as an aid to ophthalmic surgery.

References.

1. Werner L, *et al.* Permanent blue discoloration of a hydrogel intraocular lens by intraoperative trypan blue. *J Cataract Refract Surg* 2002; **28:** 1279–86.
2. Eartogiou C, *et al.* Functional outcome after trypan blue-assisted vitrectomy for macular pucker: a prospective, randomized, comparative trial. *Am J Ophthalmol* 2004; **138:** 1–5.
3. Gouws P, *et al.* Cystoid macular oedema with trypan blue use. *Br J Ophthalmol* 2004; **88:** 1348–9.
4. Lee KL, *et al.* A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery. *Br J Ophthalmol* 2005; **89:** 420–4.
5. Healey PR, Crowston JG. Trypan blue identifies endometabolite treatment area in trabeculectomy. *Br J Ophthalmol* 2005; **89:** 1152–6.
6. Roos JC, Kerr Muir MG. Use of trypan blue for penetrating keratoplasty. *J Cataract Refract Surg* 2005; **31:** 1867–9.
7. Dick HB, *et al.* Effect of trypan blue on the elasticity of the human anterior lens capsule. *J Cataract Refract Surg* 2008; **34:** 1367–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Oftalblu†; *Neth.*: MembraneBlue†; VisionBlue; *USA*: MembraneBlue; VisionBlue.

Trypsin *(BAN)* ⊗

EC 3.4.21.4; Thrypsinum; Tripsina; Tripsinas; Tripszin; Trypslini; Trypsine; Trypsinum; Trypsyna; Трипсин.

CAS — 9002-07-7.

ATC — B06AA07; D03BA01.

ATC Vet — QB06AA07; QD03BA01.

UNII — GV54A213NN (trypsin); 57I8NCH27R (bovine trypsin); V6GZ69J3FW (porcine trypsin).

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

Ph. Eur. 8: (Trypsin). A proteolytic enzyme obtained by the activation of trypsinogen extracted from mammalian pancreas. It has an activity of not less than 0.5 microkatals/mg, calculated with reference to the dried substance. A white or almost white, crystalline or amorphous powder; the amorphous form is hygroscopic. Sparingly soluble in water. A 1% solution in water has a pH of 3.0 to 6.0. Solutions have a maximum stability at pH 3 and a maximum activity at pH 8. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Crystallized Trypsin). A proteolytic enzyme crystallised from an extract of the pancreas of healthy bovine or porcine animals, or both. It contains not less than 2500 USP units in each mg, calculated on the dried basis. A white to yellowish-white, odourless, crystalline or amorphous powder. Store in airtight containers at temperature not exceeding 40 degrees.

Profile

Trypsin is a proteolytic enzyme that has been applied for the debridement of wounds. It has also been taken orally, usually with chymotrypsin (p. 2477.3), and sometimes with antibacterial or other drugs, for its supposed benefit in relieving oedema and inflammation associated with infection or trauma. Trypsin solutions have been inhaled for the liquefaction of viscous sputum, and trypsin is also an ingredient of mixtures intended to relieve various gastrointestinal disorders. Trypsin has been used in oncology in a combination preparation with chymotrypsin and papain (see under Uses and Administration of Papain, p. 2583.1).

Hypersensitivity reactions may occasionally occur.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Leukase†; Phlogenzym; Rutozym; Traumazym; Wobenzym; *Braz.*: Parenzyme Analgesico; Parenzyme†; *Canad.*: Wobenzym; *China*: YiMei (怡美); *Cz.*: Phlogenzym; Wobenzym; *Ger.*: Phlogenzym†; Wobenzym plus; *Gr.*: Chymoral; Itastab; Tricuval; *Hung.*: Phlogenzym; *India*: Alfapsin; Ceze; Chymase; Chymin; Chymobel Plus; Chymobel; Chymoral; Chymosoz-D; Chymotas; Chymotrip; Chymutrip; Disperzyme; Enractin; Fido-Forte; Flamotryp; K-Trip Plus; K-Trip; Kymovil Plus; Omotrip; Optase-DC; Orthal Forte; Orthotime; Soluzyme; *Jpn*: Kimotab†; *Mex.*: Ochozim; Phlogenzym; Quimotrip†; Ribotripsin; Wobe-Mugos; Wobenzym; Zimotris; *Port.*: Anginova; Chimar; *Rus.*: Phlogenzym (Флогэнзим); Wobe-Mugos E (Вобэ-Мугос Е); Wobenzym (Вобэнзим); *Spain*: Dertrase; Dosil Enzimatico; Doxiten Enzimatico; Kanapomada†; Naso Pekamin†; Quimodril; *Ukr.*: Phlogenzym (Флогэнзим); Wobe-Mugos E (Вобэ-Мугос Е)†; Wobenzym (Вобэнзим); *USA*: Allanderm-T†; Bio-Zyme; Dermuspray; Granulderm†; Granulex; GranuMed; Optase; Vasolex; Xenaderm; *Venez.*: Phlogenzym; Wobenzym N.

Tuberculins

Tuberculinas; Туберкулины.

ATC — V04CF01.

ATC Vet — QV04CF01.

NOTE. 'PPD' is an abbreviation sometimes used for tuberculin purified protein derivative which should not be confused with paraphenylenediamine (p. 2583.2), which is also referred to by the same abbreviation.

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

Ph. Eur. 8: (Tuberculin for Human Use, Old). It consists of a filtrate, concentrated by heating, containing the soluble products of the culture and lysis of one or more strains of *Mycobacterium tuberculosis* and/or *M. bovis*. It contains a suitable preservative that does not give rise to false-positive reactions. In concentrated form, it is a transparent, viscous, yellow or brown liquid. Protect from light.

Ph. Eur. 8: (Tuberculin Purified Protein Derivative for Human Use). A preparation obtained by precipitation from the heated products of the culture and lysis of *Mycobacterium tuberculosis* and/or *M. bovis*. It contains a suitable preservative that does not give rise to false-positive reactions. It is a colourless or pale yellow liquid; the diluted preparation may be a freeze-dried powder which upon dissolution gives a colourless or pale yellow liquid. Protect from light.

Uses and Administration

Tuberculin skin tests are used to detect tuberculoprotein hypersensitivity when BCG vaccination is being considered or as an aid to diagnosis of tuberculosis. A person showing a specific sensitivity to tuberculin is considered to have been infected with the tubercle bacillus, though the infection may be inactive. Tuberculin for sensitivity testing is given by intradermal injection as in the Mantoux test. Multiple-puncture devices such as the Heaf test or tine tests have also been used, although they are no longer available in the UK.

In the UK, it is recommended that tuberculin testing should always be performed when BCG vaccination is being considered, and the **Mantoux** test is recommended. For a routine Mantoux test, a diluted solution (2TU/0.1 mL) of tuberculin purified protein derivative (PPD) is given by intradermal injection and the reaction, which is graded by the transverse diameter of the area of induration, read 48 to 72 hours later. A retest with a stronger solution (10TU/0.1 mL) of PPD may be considered if the results of the initial test are unclear.

Individuals with a negative reaction (induration of less than 6 mm) who have not previously been given BCG vaccines may be offered BCG vaccination. Patients with a reaction (induration of 6 mm or greater) are considered to be positive (hypersensitive) to tuberculoprotein and should not be vaccinated. Investigation for the presence of active tuberculosis is generally only indicated for patients showing a strongly positive reaction (induration 15 mm and above) to a tuberculin skin test. However, there are many factors that should be considered when interpreting the results; in addition to those listed under Precautions (see p. 2636.2), there are the effects of previous BCG vaccination, repeated tuberculin testing, and age. In some areas, a positive reaction may be a result of cross-sensitivity of the test to non-tuberculous mycobacteria (see p. 2636.1).

For the **Heaf** test, a solution of PPD is applied to the forearm using a multiple-puncture gun (Heaf gun), and the reaction evaluated about a week later.

The term **tine** test is generally used for disposable multiple-puncture devices coated with dried old tuberculin or PPD. However, some consider tine tests to be unreliable.

In some other countries, the population tested, the procedures used, and grading of reactions may differ slightly from that outlined above.

Tuberculins have also been used with other antigens for anergy testing to assess the status of cell-mediated immunity.

Latent tuberculosis. Full eradication of tuberculosis from developed countries requires identification of latent as well as active cases.[1] Tuberculin testing has been in use for over 100 years and, while still considered a useful diagnostic agent for tuberculosis, the problems of false-positive reactions or reduced sensitivity to the test are well recognised.[1] Use of the test to identify latent disease has evolved with experience.[2] Previous BCG vaccination is one factor that significantly increases the likelihood of a false-positive reaction to tuberculin testing, which makes the diagnosis of latent tuberculosis particularly difficult.[3] Interpretation of the skin test should therefore be made by considering the induration size in the context of the individual clinical profile, including other risk factors for infection.[2,3] Three different approaches to assess the annual risk of tuberculous infection using tuberculin testing gave different results in a study of schoolchildren who had been given BCG vaccinations early in life.[4] This led the authors to conclude that the effect of previous BCG vaccination on tuberculin reactivity may be more complex than assumed, and that the tuberculin test is a poor indicator of latent infection. It has been suggested[2] that it is not necessary for low-risk persons in the general population of the USA to receive routine tuberculin testing for tuberculosis; high-risk groups of adults and children for whom screening might be warranted have been defined, and consensus recommendations made.

1. Lee E, Holzman RS. Evolution and current use of the tuberculin test. *Clin Infect Dis* 2002; **34**: 365–70.
2. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. 1999. Available at: http://www.thoracic.org/statements/resources/mtpi/latenttb1-27.pdf (accessed 16/08/10)
3. Wang L, *et al.* A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax* 2002; **57**: 804–9. Correction: *ibid.* 2003; **58**: 188.
4. Leung CC, *et al.* Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. *Thorax* 2005; **60**: 124–9.

Malignant disease. Benefit has been reported[1] in 2 patients with adult T-cell leukaemia/lymphoma mainly involving the skin after local treatment with tuberculin purified protein derivative.

1. Kanekura T, *et al.* Purified protein derivative treatment for skin lesions of adult T-cell leukaemia/lymphoma. *Br J Dermatol* 1999; **140**: 767–8.

Non-tuberculous mycobacterial infection. The tuberculin skin test is not specific for *Mycobacterium tuberculosis*, but can also represent a cross-reaction caused by antigens on other non-tuberculous mycobacteria. Re-examination[1] of results from children with non-tuberculous mycobacterial infection concluded that the avian Mantoux test (avian tuberculin purified protein derivative (PPD) prepared from *M. avium*) was more sensitive than the human Mantoux test (tuberculin PPD prepared from *M. tuberculosis*) in the detection of non-tuberculous mycobacteria in regions with a low incidence of tuberculosis, and may be a useful aid to differential diagnosis in areas where tuberculosis is prevalent.

1. Daley AJ, Isaacs D. Differential avian and human tuberculin skin testing in non-tuberculous mycobacterial infection. *Arch Dis Child* 1999; **80**: 377–9.

Adverse Effects

Pain and pruritus may occur at the injection site, occasionally with vesiculation, ulceration, or necrosis in highly sensitive persons. Granuloma has been reported.

Nausea, headache, dizziness, malaise, rash, urticaria, oedema, and pyrexia have been reported occasionally; immediate systemic hypersensitivity, including anaphylaxis, has been reported rarely. There have also been rare reports of lymphangitis.

Hypersensitivity. There are rare reports[1-4] of severe anaphylactic or anaphylactoid reactions, occasionally fatal,[1] to tuberculin.

1. DiMaio VJM, Froede RC. Allergic reactions to the tine test. *JAMA* 1975; **233**: 769.
2. Spiteri MA, *et al.* Life threatening reaction to tuberculin testing. *BMJ* 1986; **293**: 243–4.
3. Wright DN, *et al.* Systemic and local allergic reactions to the tine test purified protein derivative. *JAMA* 1989; **262**: 2999–3000.
4. Sanofi Pasteur, Canada. Risk of serious allergic reactions following TUBERSOL [Tuberculin Purified Protein Derivative (Mantoux)] administration (issued 19th May 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tubersol_hpc-cps-eng.pdf (accessed 08/08/08)

Lymphangitis. Lymphangitis has been reported on 5 occasions after the Mantoux test and on 7 occasions after the Heaf test.[1] However, it was noted that a tuberculin test may have been inappropriate in some of these patients, particularly older subjects and those with evidence of healed tuberculous lesions.[2]

1. Morrison JB. Lymphangitis after tuberculin tests. *BMJ* 1984; **289**: 413.
2. Festenstein F. Lymphangitis after tuberculin tests. *BMJ* 1984; **289**: 625–6.

Precautions

Tuberculin should be given with caution to patients who have, or are suspected of having, active tuberculosis; although severe local reactions may occur in patients with active tuberculosis, sensitivity may be diminished if it is particularly severe. Sensitivity to tuberculin may also be diminished in the following conditions: viral or severe bacterial infection including HIV infection and infectious mononucleosis; neoplastic disease particularly lymphoma; sarcoidosis; corticosteroid or immunosuppressive therapy; recent use of live virus vaccines; ultraviolet light treatment; chronic renal failure; dehydration; and malnutrition.

Tuberculins may be adsorbed onto the surface of syringes and should therefore be given immediately.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tuberculin PPD 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 20/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Tubersol; *Fr.*: Tubertest; *Gr.*: Imotest Tuberculin; *India*: Monotest; *Israel*: Tubersol; *Ital.*: Biocine Test PPD†; *NZ*: Tubersol; *S.Afr.*: Biocine Test†; Japan Freeze-Dried Tuberculin†; *USA*: Aplisol; Tubersol.

Multi-ingredient Preparations. *Austral.*: Multitest CMI†; *Gr.*: Multitest.

Homoeopathic Preparations. *Ger.*: metabiarex.

Pharmacopoeial Preparations
Ph. Eur.: Old Tuberculin for Human Use; Tuberculin Purified Protein Derivative for Human Use.

Tucaresol *(BAN, rINN)* ⊗

589C; 589C80; BW-589C; Tucarésol; Tucaresolum; Тукарезол.
α-(2-Formyl-3-hydroxyphenoxy)-*p*-toluic acid.
$C_{15}H_{12}O_5$=272.3
CAS — 84290-27-7.
UNII — JH368G5B9M.

Profile

Tucaresol is reported to interact with haemoglobin to increase oxygen affinity. It has been investigated as an oral drug for the treatment of sickle-cell disease (p. 1123.2). Tucaresol is also reported to have immunostimulant properties and is under investigation in HIV infection and hepatitis B. Hypersensitivity reactions have occurred.

References.

1. Rolan PE, *et al.* The pharmacokinetics, tolerability and pharmacodynamics of tucaresol (589C80; 4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects. *Br J Clin Pharmacol* 1993; **35**: 419–25.
2. Arya R, *et al.* Tucaresol increases oxygen affinity and reduces haemolysis in subjects with sickle cell anaemia. *Br J Haematol* 1996; **93**: 817–21.
3. Peck RW, *et al.* Effect of food and gender on the pharmacokinetics of tucaresol in healthy volunteers. *Br J Clin Pharmacol* 1998; **46**: 83–6.
4. Gori A, *et al.* Immunomodulation induced by tucaresol in HIV infection: results of a 16 week pilot Phase I/II trial. *Antivir Ther* 2004; **9**: 603–14.

Javanese Turmeric

Curcuma Zanthorrhiza; Curcumae Javanicae; Curcumae xanthorrhizae rhizoma; Geltonšaknių ciberžolių šakniastiebiai; Gurkmeja, javanesisk; Jaavan kurkuma; Jávai-kurkuma gyökértörzs; Oddenek kurkumy žlutokořenné; Temoe lawacq; Temoe Lawak; Témoé-lawaq; Куркума Яванская.
ATC Herb — HA03AW5021 (Curcuma zanthorrhiza: rhizome); HA05AW5006 (Curcuma zanthorrhiza: rhizome).
UNII — SD3M9QA214.

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

Ph. Eur. 8: (Turmeric, Javanese). It consists of the dried rhizome, cut in slices, of *Curcuma xanthorrhiza*. It contains not less than 5% v/w of essential oil and not less than 1% of dicinnamoyl methane derivatives expressed as curcumin, both calculated with reference to the anhydrous drug. It has an aromatic odour. Protect from light.

Profile

Javanese turmeric is an ingredient of preparations indicated for biliary and gastrointestinal disorders. It is a close relative of the spice turmeric (p. 2218.1), which has been used similarly.

Irritable bowel syndrome. For reference to the ineffectiveness of Javanese turmeric in patients with irritable bowel syndrome see under Fumitory, p. 2508.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Curcu-Truw; Pankreaplex mono.

Multi-ingredient Preparations. *Austria*: Choleodoron; *Canad.*: Gallexier†; *Fr.*: Hepaclem†; Kotor Articulations; *Ger.*: Bilisan Duo†; Enzym-Harongan; Gallexier; Gallexier; Hevert Stoffwechsel-Tee N†; Infi-tract V; *Hong Kong*: Hepatofalk Planta†; Hepatofalk†; *Indon.*: Curbexon; Curliv Plus; Curliv Plus; Curliv; Cursil; Curson†; Gramuno; Hepa-Q; Hepacell†; Hepasitin; Hepatofalk Planta†; Hepimun Plus; Hepimun; Librozym†; Norflam; Nutrijoint; Picula; Verona; *S.Afr.*: Choleodoron†; *Singapore*: Hepatofalk Planta†; *Switz.*: Choleodoron.

Homoeopathic Preparations. *Canad.*: Choleodoron†; *Fr.*: Choleodoron; *Ger.*: Choleodoron†; *Neth.*: Choleodoron; *UK*: Choleodoron.

Turpentine Oil

Aetheroleum Terebinthinae; Esencia de Trementina; Essence de Térébenthine; Oleum Terebinthinae; Oleum Terebinthinae Depuratum; Rectified Turpentine Oil; Spirits of Turpentine; Térébenthine, huile essentielle de; Terebentin, Yağı; Terebinthini aetheroleum; Terebintin Esansı; Trementina, aceite esencial de; Скипидар; Терпентинное Масло.
ATC Herb — HM02AW5014 (Pinus pinaster: essential oil).
UNII — C5H0QJ6V7F.

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

Ph. Eur. 8: (Turpentine Oil, Pinus Pinaster Type; Terebinthini Aetheroleum ab Pinum Pinastrum). An essential oil obtained by steam distillation, followed by rectification at a temperature below 180 degrees, from the oleoresin obtained by tapping *Pinus pinaster*. A suitable antoxidant may be added. It contains 70.0 to 85.0% α-pinene, 0.5 to 1.5% camphene, 11.0 to 20.0% β-pinene, maximum 1% car-3-ene, 0.4 to 1.5% β-myrcene, 1.0 to 7.0% limonene, 0.2 to 2.5% longifolene, 0.1 to 3.0% β-caryophyllene, and maximum 1.0% caryophyllene oxide.

A clear, colourless or pale yellow liquid with a characteristic odour. Relative density 0.856 to 0.872. Store in well-filled airtight containers at a temperature not exceeding 25 degrees. Protect from light.

Uses and Administration

Turpentine oil is widely used as a solvent. It is applied topically as a rubefacient. It is an ingredient of many preparations used in respiratory-tract disorders, but is now judged to be neither safe nor effective.

Adverse Effects

In poisoning with turpentine oil there may be local burning and gastrointestinal upset, coughing and choking, pulmonary oedema, excitement, coma, fever, tachycardia, liver damage, haematuria, and albuminuria. Fatalities have occurred.

The application to the skin of liniments containing turpentine oil may cause irritation and absorption of large amounts may cause some of the effects listed above. Hypersensitivity reactions and local irritation have been reported.

References.

1. Khan AJ, *et al.* Turpentine oil inhalation leading to lung necrosis and empyema in a toddler. *Pediatr Emerg Care* 2006; **22**: 355–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Ozothine; *Port.*: Vicks Vaporub.

Multi-ingredient Preparations. *Arg.*: Adhesol; Atomo Desinflamante C; Bronco Etersan; Cerax; Fluido Spineda; Notoxin; Novobroncol; Otocalmia; Rati Salil Crema; *Austral.*: Goanna Heat Cream; Goanna Oil Liniment; Goanna Salve†; Vicks Vaporub; *Austria*: Acimont; Baby Luuf atherische Ole; Baby Luuf; Bronchostop†; Carl Baders Divinal; Ilon Abszess; Kinder Luuf; Luuf Balsam; Pe-Ce†; Piniment; Piniment; Piniment; Rubriment; Scottopect; Trauma-Salbe warmend; Tussamag; Vulpuran; Wick Vaporub; *Belg.*: Algis-Spray; Reflexspray; Vicks Vaporub; *Braz.*: A Curitybina; Aliviol; Angino-Rub; Benegel; Prixopel; Gelflex; Gelo-Bio; Gelofrix; Massageol; Nevrol†; Prati-

gel; Traumac†; Traumagel; Vick Vaporub; *Canad.*: Cal Mo Dol†; Cerumol; Hot Stuff†; *Chile*: Calorub Nueva Formula; Hansaplast Descongestionante†; Mentobalsam†; *China*: Zheng Tong Gao (正通膏); *Cz.*: Ilon Abszess; *Fin.*: Vicks Vaporub; *Fr.*: Activox; Lumbalgine; Ozothine a la Diprophylline; Ozothine†; Respirea†; Vicks Vaporub; *Ger.*: Erkaltungs Bad N†; Grippostad Erkaltungsbalsam; Ilon Abszess; Kneipp Rheumabad Spezial†; tactu-mobil; Tetesept Erkaltungs Bad; Wick Vaporub; *Gr.*: Deep Heat; EKS; Faragel-Forte; Ilon; Pinimenthol; Revigel; Santoux; Vicks Vaporub; *Hung.*: Baby Luuf; Deep Heat Rub; Kinder Luuf Balsam; *India*: Artrex; Ceruklin; Clearwax; Desol; Despol; Dewax; Diclowin; Fastwax; Flexi-muv†; Lima; Nayawax; Neurophen; Nill-O-Wax; Otoclean; Otorex; Parabec; Systaflam; Waxolve†; *Indon.*: Opino†; Sloan's Liniment†; *Irl.*: Deep Heat; Menthol & Wintergreen; Vicks Vaporub; *Israel*: Deep Heat Rub; Ment-O-Cap†; *Ital.*: Capsolin; Vicks Vaporub; *Malaysia*: Thermorub†; *Neth.*: Luuf Verkoudheidsbalsem (voor baby's); Luuf Verkoudheidsbalsem (voor kinderen); Luuf Verkoudheidsbalsem; Vicks Vaporub; *NZ*: Vicks Vaporub; *Pol.*: Analgol; Analgolan; Capsigel N; Derhotill; Dip Hot; Herbolen†; Inhalol; Neo-Capsiderm; Pulmonil; Reumatik; Rub-Arom; Wick Vaporub; *Port.*: Balsamo Analgesico Basi; Balsamo Analgesico Labesfal; Callcida Indiano; *Rus.*: Alvipsal (Алвипсал); Capsicam (Капсикам); Carmolis Fluid (Кармолис Жидкость); Deep Heat (Дип Хит); Doktor Mom (Доктор Мом); Mentholatum (Ментолатум); Moov (Муув); Nigvisal B (Нижвисал B); Salvisar (Салвисар); Suprima-Plus (Суприма-Плюс); Viprosal B (Випросал B); *S.Afr.*: Balsem Sulphuris; Deep Heat Rub†; Haarlemensis; Puma Balm; Respisniffers†; Sloan's Liniment Rub†; Vicks Vaporub†; Woodwards Inhalant; *Singapore*: Woodward's Baby Chest Rub; *Spain*: Arkoresp†; Embrocadon Gras†; Masagil†; Otocerum; Reflex; Termosan; *Swed.*: Vicks Vaporub; *Switz.*: Baume du Chalet; Cerumenol; Eucapinol; Knobel Huile N†; PO-HO bleu; Pommade au Baume; Vicks Vaporub N; *Thai.*: Stoke'Liniment Sahakarn; Stopain; U-Gesic Balm; *Turk.*: Algo-Wax; Antidot; Bugumentol; Buguseptil; Capsalgine; Gelocaps; Kataljin; Vicks Vaporub; *UK*: Deep Heat Rub; Dragon Balm; Ellimans; Goddards Embrocation; Gonne Balm; Modern Herbals Muscular Pain; Nasciodine; Nine Rubbing Oils; Vicks Vaporub; *Ukr.*: Capsicam (Капсикам); Deep Heat (Дип Хит); Doktor Mom (Доктор Мом); Helpex Effect (Хелпекс Эффект); Ilon (Илон); Viprosal B (Випросал B); *USA*: Vicks Vaporub.

Homoeopathic Preparations. *Ger.*: Cysto-cyl L Ho-Len-Complex; uro-loges; *Neth.*: Enulite; *Rus.*: Helidonium-Plus (Хелидониум-Плюс).

Pharmacopoeial Preparations
BP 2014: White Liniment.

Tyramine Hydrochloride ⊗

Tiramina, hidrocloruro de; *p*-Tyramine Hydrochloride; Tyrosamine Hydrochloride; Тирамина Гидрохлорид.
4-Hydroxyphenethylamine hydrochloride; 4-(2-Aminoethyl) phenol hydrochloride.
$C_8H_{11}NO,HCl$=173.6
CAS — 51-67-2 (tyramine); 60-19-5 (tyramine hydrochloride).
UNII — Z5KDH3H147.

Profile

Tyramine hydrochloride is a sympathomimetic with indirect effects on adrenergic receptors. It has been given orally or by injection in the tyramine pressor test for the investigation of monoamine oxidase inhibitory activity or amine uptake blocking activity. It has also been used in studies of physiological and disease states, and in the diagnosis of migraine and phaeochromocytoma.

The hazards of consuming foods rich in tyramine while taking MAOIs are described under Phenelzine, p. 444.3.

The bioavailability of oral tyramine is significantly reduced by the presence of food, which could have implications when used in tyramine pressor tests.[1]

1. VanDenBerg CM, *et al.* Tyramine pharmacokinetics and reduced bioavailability with food. *J Clin Pharmacol* 2003; 43: 604–9.

Ubidecarenone *(BAN, rINN)*

Coenzima Q-10; Coenzyme Q10; Ubidecarenon; Ubidecarenona; Ubidécarénone; Ubidecarenonum; Ubidekarenon; Ubidekarenonas; Ubidekarenoni; Ubiquinona-10; Ubiquinone-10; Убидекаренон.
2-Deca(3-methylbut-2-enylene)-5,6-dimethoxy-3-methyl-*p*-benzoquinone.
$C_{59}H_{90}O_4$=863.4
CAS — 303-98-0.
ATC — C01EB09.
ATC Vet — QC01EB09.
UNII — EJ27X76M46.

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

Ph. Eur. 8: (Ubidecarenone). A yellow or orange crystalline powder. It gradually decomposes and darkens on exposure to light. M.p. about 48 degrees. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in acetone. Store in airtight containers. Protect from light.

USP 36: (Ubidecarenone). A yellow to orange, crystalline powder. M.p. about 48 degrees. Practically insoluble in water; very slightly soluble in dehydrated alcohol; soluble in ether. Protect from light.

Profile

Ubidecarenone is a naturally occurring coenzyme involved in electron transport in the mitochondria. It is claimed to be a free radical scavenger and to have antioxidant and membrane stabilising properties. It has been given orally as an adjunct in cardiovascular disorders, including mild or moderate heart failure. It has also been tried in other conditions associated with coenzyme deficiency, and is promoted as a dietary supplement. Ubidecarenone is under investigation for the management of cancer, Huntington's chorea (p. 1029.3) and parkinsonism.

For a discussion of the use of ubidecarenone in statin-induced muscle disorders, see Effects on Skeletal Muscle, under Simvastatin, p. 1493.2.

References.
1. Greenberg S, Frishman WH. Co-enzyme Q_{10}: a new drug for cardiovascular disease. *J Clin Pharmacol* 1990; 30: 596–608.
2. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; 344: 1372–3.
3. Garcia Silva MT, *et al.* Improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1994; 343: 1039.
4. Gattermann N, *et al.* No improvement of refractory sideroblastic anaemia with ubidecarenone. *Lancet* 1995; 345: 1121–2.
5. Nagao T, *et al.* Treatment of warfarin-induced hair loss with ubidecarenone. *Lancet* 1995; 346: 1104–5.
6. Pepping J. Coenzyme Q_{10}. *Am J Health-Syst Pharm* 1999; 56: 519–21.
7. Khatta M, *et al.* The effect of coenzyme Q_{10} in patients with congestive heart failure. *Ann Intern Med* 2000; 132: 636–40.
8. Tran MT, *et al.* Role of coenzyme Q10 in chronic heart failure, angina, and hypertension. *Pharmacotherapy* 2001; 21: 797–806.
9. Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 2001; 57: 397–404.
10. Rahman S, *et al.* Neonatal presentation of coenzyme Q10 deficiency. *J Pediatr* 2001; 139: 456–8.
11. Roffe L, *et al.* Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review. *J Clin Oncol* 2004; 22: 4418–24.
12. Sándor PS, *et al.* Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005; 64: 713–15.
13. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q_{10} during statin therapy. *Ann Pharmacother* 2006; 40: 290–4.
14. The NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q_{10} and GPI-1485 in early Parkinson disease. *Neurology* 2007; 68: 20–8.
15. Rosenfeldt FL, *et al.* Coenzyme Q_{10} in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens* 2007; 21: 297–306.
16. Ho MJ, *et al.* Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/07/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: QX 100; *Braz.*: Vinocard Q10; *Canad.*: CoQuinone; Ultra COQ10†; *China*: Fu Xin (辅辛); He Fu (合夫); Neuquinon (能气朗); *Fr.*: Q10; *Hong Kong*: CoQuinone†; Eiquinon; *Hung.*: Myoqinon; Q-Gel; *India*: Atp; Co.Q.Care; Coq; Coten; Miraqule; *Indon.*: Co-En Q; Coten; Enzimten; Nuzym; Q-Ten; Qubi; Ubi-Q; VQ; *Ital.*: Decafar†; Decorenone; Oropigma Gel; Tricoxen; Ubicor; Ubidenone†; Ubidex†; Ubimaior; *Jpn*: Neuquinon; *Malaysia*: Alerten; Bio-Quinone; Eurobio BioQ-10; Neuquinon; *Mex.*: CoQuinone; *Philipp.*: Addlife; Alerten; EssenVida; Neuquinon; *Pol.*: Envit Q_{10}†; Vita Care Q_{10}; *Port.*: Q 10; Ubenzima; *Rus.*: Qudesan (Кудесан); *Singapore*: Alerten; CoQuinone†; Ubi-Q; Vita Co-Enzyme Q10; *Thai.*: Alerten; Bio Q10 VQ50; Bio-Quinone; Decaquinon; VQ†; *UK*: Bio-Quinone; *USA*: CoQuinone.

Multi-ingredient Preparations. *Arg.*: Cardiobiotral; Desgras Piel Naranja; Marathon Antioxidante; Marathon; QX 10; *Austral.*: CardiWell Omega Q10; Homme-F; Proactive Multi for 50+; Radiance; *Belg.*: Ostrin Q10; *Canad.*: Clear Q†; Mega AO; Protect†; Support Formula†; *Chile*: Eucerin Q10 Active; Infor Q10; Logical; Marathon; Trivitana Q10; Ubiten; Ultrac Q10; Ureadin Facial Antarrugas; *Fr.*: Arterin Plus; Microbiane Q10; *Hong Kong*: Cardiozen; *Hung.*: Q_{10}; *India*: Bio-10; Cardi-NRG; Cardio-Pro; Co-Q-Dent; Coq Forte; Ecozyme; Enhance; Hairstim-HGF; Hepa; Hi-Q Plus; Hi-Q; Hyrase; I-10; I-Vit Plus; Imunolife; Jivak; Jstat; Liveril; Maxoza; *Indon.*: Baliin Q10; Bioquinone; Canergy†; Car-Q; Carnon; Co-Q-10; Co-vitala; Combes†; Cor-Q; Corsel; Enercore; Galten; Life 10; Liproqy; Lycoq†; Metsel; nu Qten Com; Qutan-10; RG-Q; *Ital.*: Anasten Plus; Berart; Coqun; Diaberet; Linfolipase; Ocustress; Phototrop; Salovit; Selemix; Visu Q10; VisuQ10; Vitalmix Complex; Vitalmix Fos; *Malaysia*: Hovid Q-10 SupraBio + L-Carnitine; Hovid Q10 Plus†; *Mex.*: Avitil; *Philipp.*: Havitall; Immuvit; Nutrotal; Polynerv-E with lecithin; SafeStat; *Singapore*: Cardio-Essentials; Co3E + CoQ10; Enerbolis; Espanone; Essentials†; RejuvaSkin Anti-Aging Serum; Scar Esthetique; *UK*: Neurozan; NutriScience; Red Kooga Co-Q-10 and Ginseng; *Ukr.*: Perfectil Plus (Перфектил Плюс); Vitrum Beauty Q10 (Витрум Бьюти Q10)†; *USA*: AquADEKS; Cardio Tone; Corvite Free; Diabetiks; PreQue 10; ProtectNatal; Triveen-Ten; *Venez.*: Uvagen.

Pharmacopoeial Preparations
USP 36: Ubidecarenone Capsules; Ubidecarenone Tablets.

Ulinastatin *(rINN)*

Ulinastatina; Ulinastatine; Ulinastatinum; Urinastatin; Улинастатин.
CAS — 80449-31-6; 80449-32-7.

Pharmacopoeias. In *Jpn*.

Profile

Ulinastatin is a glycoprotein proteolytic enzyme inhibitor isolated from human urine. It has been given by slow intravenous injection or by intravenous infusion in acute pancreatitis (p. 2580.2) and in acute circulatory insufficiency.

References.
1. Ohwada M, *et al.* New endoscopic treatment for chronic pancreatitis, using contrast media containing ulinastatin and prednisolone. *J Gastroenterol* 1997; 32: 216–21.
2. Sugita T, *et al.* Effect of a human urinary protease inhibitor (Ulinastatin) on respiratory function in pediatric patients undergoing cardiopulmonary bypass. *J Cardiovasc Surg* 2002; 43: 437–40.
3. Tsujino T, *et al.* Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005; 3: 376–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Luo An (洛安); *Jpn*: Miraclid.

Uracil *(USAN)*

BMS-205603-01; Sq-6201; Sq-7726; Sq-8493; Урацил.
2,4(1*H*,3*H*)-pyrimidinedione.
$C_4H_4N_2O_2$=112.1
CAS — 66-22-8.
UNII — 56HH86ZVCT.

Profile

Uracil is a pyrimidine base and one of the components of uridine nucleotides that form ribonucleic acid (p. 2604.1). It inhibits dihydropyrimidine dehydrogenase and reduces the metabolism of fluorouracil; it is given orally with tegafur (p. 864.2), an oral fluorouracil prodrug, to increase the bioavailability of fluorouracil.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Asofurtal; Fimer; UFT; *Austria*: UFT; *Belg.*: UFT; *Braz.*: UFT; *Cz.*: UFT†; *Denm.*: UFT; Uftoral†; *Fr.*: UFT; *Ger.*: UFT; *Gr.*: UFT; *Hong Kong*: UFT†; *Hung.*: UFT†; *Irl.*: UFT†; *Israel*: UFT; *Ital.*: UFT; *Jpn*: UFT; *Malaysia*: UFT; *Mex.*: UFT; *Neth.*: UFT; *Norw.*: UFT†; *Philipp.*: Tefudex; UFT; *Pol.*: UFT; *Port.*: UFT; *Rus.*: UFT (УФТ); *S.Afr.*: UFT; *Singapore*: UFT; *Spain*: UFT†; *Swed.*: UFT†; *Thai.*: UFT†; UFUR; *Turk.*: UFT; *UK*: Uftoral†.

Urazamide

5-Aminoimidazole-4-carboxamide ureidosuccinate.
$C_9H_{14}N_6O_6$=302.2
CAS — 34879-34-0.
UNII — 671534JBYI.

Profile

Urazamide has been given orally in the treatment of hepatic disorders. It has also been given by intramuscular and intravenous injection.

Uridine

Uracil Riboside; Uridina; Urydyna; Уридин.
1-β-D-Ribofuranosyluracil; 1-β-D-Ribofuranosylpyrimidine-2,4 (1*H*,3*H*)-dione.
$C_9H_{12}N_2O_6$=244.2
CAS — 58-96-8.
UNII — WHI7HQ7H85.

Profile

Uridine is an endogenous uracil nucleoside involved in many biological processes; it is one of the components of nucleic acids (p. 2573.1). Uridine is used in preparations containing other nucleosides in the treatment of corneal damage. It has been included in preparations for peripheral and cerebral vascular disorders and myopathies; it has also been used for liver disorders, anaemias, and as a tonic. Uridine has been tried in patients with hereditary orotic aciduria.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hong Kong*: Vitacict†; *Ital.*: Centrum; *Mon.*: Vitacic.

Uridine Triphosphate

Ins-316; Trifosfato de uridina; Uridina trifosfato; Uridine Triphosphoric Acid; UTP; Уридин Трифосфат.
Uridine 5′-(tetrahydrogen triphosphate).
$C_9H_{15}N_2O_{15}P_3$=484.1
CAS — 63-39-8.

Profile

Uridine triphosphate is an endogenous uracil nucleotide involved in many biological processes. It has been claimed to be of value in muscular atrophy and muscular weakness, and has been included in preparations for neuralgia, neuritis, and muscular disorders; the disodium and trisodium salts have also been used.

Uridine triphosphate has been reported to have beneficial effects on mucociliary clearance in chronic respiratory disease such as cystic fibrosis, asthma, and chronic bronchitis, although it may not be suitable for such therapy because it is rapidly degraded by enzymatic activity within sputum and by airway epithelial cells.[1,2] It may, however, have a role as a method of producing deep-lung sputum specimens for cytological evaluation and is being investigated as an aid to the diagnosis of for example, lung cancer[1,2] or airway inflammation in asthma.[3]

1. Bennett WD, *et al.* Effect of aerosolized uridine 5′-triphosphate on mucociliary clearance in mild chronic bronchitis. *Am J Respir Crit Care Med* 2001; 164: 302–6.
2. Johnson FL, *et al.* Improved sputum expectoration following a single dose of INS316 in patients with chronic bronchitis. *Chest* 2002; 122: 2021–9.
3. Tamaoki J, *et al.* Validity and safety of sputum induction by inhaled uridine 5′-triphosphate. *Am J Respir Crit Care Med* 2001; 164: 378–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Uteplex.

Multi-ingredient Preparations. *Braz.*: Etna; Nucleo CMP; *Chile*: Citoneuron; *Mex.*: Nucleo CMP; *Spain*: Nucleo CMP; *Ukr.*: Keltican (Кетикан); Nucleo CMF Forte (Нуклео ЦМФ Форте).

Ursodeoxycholic Acid *(BAN, rINN)*

Acide Ursodéoxycholique; Acide ursodésoxycholique; Ácido ursodeoxicólico; Ácido ursodesoxicólico; Acidum ursodeoxycholicum; Kyselina ursodeoxycholová; UDCA; Ursodeoksicholio rūgštis; Ursodeoksikolik Asit; Ursodeoksikoolihappo; Ursodeoxicholsyra; Ursodeoxicólico, ácido; Ursodesoxycholic Acid; Ursodesoxycholsäure; Ursodiol (USAN); Urzodezoxikólsav; Урсодезоксихолевая Кислота.
3α,7β-Dihydroxy-5β-cholan-24-oic acid.
$C_{24}H_{40}O_4$=392.6
CAS — 128-13-2.
ATC — A05AA02.
ATC Vet — QA05AA02.
UNII — 724L30Y2QR.

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

Ph. Eur. 8: (Ursodeoxycholic Acid). A white or almost white powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol; slightly soluble in acetone.

USP 36: (Ursodiol). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether. Store in airtight containers.

Stability. References.

1. Mallett MS, *et al.* Stability of ursodiol 25 mg/mL in an extemporaneously prepared oral liquid. *Am J Health-Syst Pharm* 1997; 54: 1401–4.
2. Johnson CE, Streetman DD. Stability of oral suspensions of ursodiol made from tablets. *Am J Health-Syst Pharm* 2002; 59: 361–3.

Uses and Administration

Ursodeoxycholic acid is a naturally occurring bile acid (see p. 2457.2) present in small quantities in human bile. Ursodeoxycholic acid suppresses the synthesis and secretion of cholesterol by the liver and inhibits intestinal absorption of cholesterol. It is given orally for the dissolution of cholesterol-rich **gallstones** in patients with functioning gallbladders (see p. 2639.1). The usual dose is 6 to 12 mg/kg daily as a single bedtime dose or in 2 or 3 divided doses; obese patients may require up to 15 mg/kg daily. The daily dose may be divided unequally and the larger dose given before bedtime to counteract the increase in biliary cholesterol concentration seen overnight. The time required for dissolution of gallstones is likely to be between 6 and 24 months depending on stone size and composition. Treatment should be continued for 3 to 4 months after radiological disappearance of the stones. A dose of 300 mg twice daily may be used for the *prevention* of gallstones in patients undergoing rapid weight loss. Ursodeoxycholic acid has also been given in reduced doses in combination with chenodeoxycholic acid (p. 2475.1).

Ursodeoxycholic acid is also used in **primary biliary cirrhosis** (see below). The usual dose is 10 to 16 mg/kg daily in 2 to 4 divided doses. After the first 3 months of treatment the dose may be taken once daily in the evening.

The more hydrophilic derivative, tauroursodeoxycholic acid, has also been used.

Administration in children. For the use of ursodeoxycholic acid in children, see Chronic Liver Disease, below.

Chronic liver disease. The use of ursodeoxycholic acid in chronic liver diseases has been summarised.[1-5] There have been differing opinions of its value in primary biliary cirrhosis (below). Response has been reported in obstetric cholestasis of pregnancy,[6-10] primary sclerosing cholangitis,[11] chronic active hepatitis,[12] and viral hepatitis.[13,14] Although ursodeoxycholic acid is widely used in the treatment of obstetric cholestasis, data on its safety and efficacy in this indication are lacking, and its possible role therefore remains unclear until further larger studies have been done.[15] See also Adverse Effects and Precautions, p. 2639.2.

Ursodeoxycholic acid appears to be of benefit in liver disease associated with cystic fibrosis[16-18] and in the UK the *BNFC* recommends an oral dose of 10 to 15 mg/kg twice daily in children from 1 month to 18 years of age with this condition; alternatively the total daily dose may be given in 3 divided doses.

Ursodeoxycholic acid had initially shown some promise in the treatment of nonalcoholic steatohepatitis,[19] but a randomised, controlled study[20] failed to confirm this. There has also been some interest in the use of ursodeoxycholic acid to treat refractory graft-versus-host disease of the liver in transplant patients,[21] and possibly as an adjuvant to immunosuppressant therapy[22-24] after orthotopic liver transplantation (p. 1936.3). It may also be of benefit in the prevention of hepatic complications following allogeneic bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p. 1933.1).[25,26]

Ursodeoxycholic acid has shortened the clinical course of parenteral nutrition-associated cholestasis in very-low-birth-weight infants,[27] and benefit has also been reported[28] in children and adults, although the optimal timing and duration of therapy remains to be evaluated. The *BNFC* recommends an oral dose of 10 mg/kg three times daily for neonates and all children up to 18 years of age for cholestasis associated with total parenteral nutrition.

Ursodeoxycholic acid has also been associated with a lower incidence of colonic dysplasia in patients with ulcerative colitis and primary sclerosing cholangitis.[29,30] For sclerosing cholangitis in children from 1 month to 18 years of age, the *BNFC* recommends an oral dose of 5 to 10 mg/kg 2 or 3 times daily up to a maximum of 15 mg/kg 3 times daily depending on response.

In children with cholestatic conditions such as familial intrahepatic cholestasis and biliary atresia, ursodeoxycholic acid may be used to improve bile flow. The *BNFC* recommends an oral dose of 5 mg/kg three times daily in neonates and children up to 2 years of age, the dose and frequency adjusted according to response up to a maximum of 10 mg/kg three times daily. Ursodeoxycholic acid has also been shown to improve liver function for several years when given to children after successful surgery for biliary atresia.[31]

1. de Caestecker JS, *et al.* Ursodeoxycholic acid in chronic liver disease. *Gut* 1991; 32: 1061–5.
2. Rubin RA, *et al.* Ursodiol for hepatobiliary disorders. *Ann Intern Med* 1994; 121: 207–18.
3. Kowdley KV. Ursodeoxycholic acid therapy in hepatobiliary disease. *Am J Med* 2000; 108: 481–6.
4. Trauner M, Graziadei IW. Review article: mechanisms of action and therapeutic applications of ursodeoxycholic acid in chronic liver diseases. *Aliment Pharmacol Ther* 1999; 13: 979–95.
5. Lazaridis KN, *et al.* Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *J Hepatol* 2001; 35: 134–46.
6. Palma J, *et al.* Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol* 1997; 27: 1022–8.
7. Roncaglia N, *et al.* A randomised controlled trial of ursodeoxycholic acid and S-adenosyl-l-methionine in the treatment of gestational cholestasis. *Br J Obstet Gynaecol* 2004; 111: 17–21.
8. Kondrackiene J, *et al.* Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology* 2005; 129: 894–901.
9. Glantz A, *et al.* Intrahepatic cholestasis of pregnancy: a randomized controlled trial comparing dexamethasone and ursodeoxycholic acid. *Hepatology* 2005; 42: 1399–1405.
10. Zapata R, *et al.* Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: a 12-year experience. *Liver Int* 2005; 25: 548–54.
11. Lindor KD, *et al.* Ursodiol for primary sclerosing cholangitis. *N Engl J Med* 1997; 336: 691–5.
12. Rolandi E, *et al.* Effects of ursodeoxycholic acid (UDCA) on serum liver damage indices in patients with chronic active hepatitis: a double-blind controlled study. *Eur J Clin Pharmacol* 1991; 40: 473–6.
13. Puoti C, *et al.* Ursodeoxycholic acid and chronic hepatitis C infection. *Lancet* 1993; 341: 1413–14.
14. Angelico M, *et al.* Recombinant interferon-α and ursodeoxycholic acid versus interferon-α alone in the treatment of chronic hepatitis C: a randomized clinical trial with long-term follow-up. *Am J Gastroenterol* 1995; 90: 263–9.
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PRIMARY BILIARY CIRRHOSIS. Primary biliary cirrhosis (PBC) is a chronic liver disease of unknown aetiology that develops due to progressive destruction of small and intermediate bile ducts within the liver, subsequently evolving to fibrosis and cirrhosis. Over 90% of patients are female, usually aged between 40 and 60 years. The disease is thought to be auto-immune in nature. Most patients develop antimitochondrial antibodies that may be evident even before disease is clinically apparent.[1,2] Genetic factors and hormonal stimulation may play a role in precipitating PBC.[1,2] Infectious agents such as *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*)[2] or retroviruses[3] may be involved in the pathogenesis.

Clinical manifestations include pruritus, fatigue, jaundice, hepatomegaly, and hypercholesterolaemia leading to xanthoma formation. In late disease portal hypertension, bleeding oesophageal varices and liver failure may develop. Impaired calcium and vitamin D absorption may result in osteomalacia or osteoporosis, and fat-soluble vitamin deficiencies may occur. There may be accumulation of copper in the liver.[4] Other disorders including rheumatoid arthritis, scleroderma, thyroiditis, and Sjögren's syndrome may be associated with PBC.[1,5]

The disease is slowly progressive, with a mean survival of 8 years for symptomatic patients, and 16 years for asymptomatic individuals.[1,6] Despite its presumed autoimmune aetiology, few immunosuppressive drugs have shown any benefit,[5,7] although newer drugs such as mycophenolate mofetil, sirolimus, and tacrolimus have yet to be fully evaluated.[7]

The best-studied treatment for PBC is ursodeoxycholic acid, which is thought to replace toxic endogenous bile acids, stimulate bile acid secretion, and exert local immunosuppressive and cytoprotective effects.[1,4,5,7-9] The value of ursodeoxycholic acid is controversial: its reported therapeutic benefits in terms of delaying disease progression and the need for liver transplantation[5,10] have not been confirmed by meta-analysis[11] or systematic review,[12] although the former was, however, criticised[13,14] on the grounds that most of the studies included had follow-up periods of only 2 years. In consequence, some do not recommend its use,[11,12,15] but others still believe it to be the treatment of choice.[1,7,13,14,16] Its advocates consider that it appears to be efficacious for about 10 years and improves long-term survival by delaying the progression of hepatic fibrosis, development of oesophageal varices, and the need

for liver transplantation. However, it is not effective in the presence of extensive fibrosis or cirrhosis in advanced disease.[13,14,16]

Both penicillamine and azathioprine have been used in PBC, but studies have failed to show any benefit from treatment[5-7] and their use has declined. A systematic review[17] identified a significant increase in the occurrence of adverse effects with penicillamine and concluded that its use could not be supported for patients with PBC. Corticosteroids, colchicine, ciclosporin, and chlorambucil have also been tried, but toxicity has restricted their use.[5,7] They may be of benefit[2,4,6,7] when used with ursodeoxycholic acid, although some guidelines[5] do not recommend their use. A systematic review[18] of studies with methotrexate concluded that it had no effect on mortality or the need for liver transplantation and should not therefore be used in patients with PBC outside clinical studies. Budesonide[7] and bezafibrate[1,7] have also been tried.

Symptomatic treatment includes the use of bile acid sequestrants, such as colestyramine, to treat both pruritus and hypercholesterolaemia. Ursodeoxycholic acid may also improve pruritus in up to 40% of patients, and rifampicin, phenobarbital, and opioid antagonists are used as second-line therapies.[1,4,5,8] Vitamin D and calcium supplementation will prevent osteomalacia; supplementation with vitamins A, E, and K may also be necessary.[1,4,5,8] Liver transplantation is recommended for liver failure, although PBC can recur in the allograft.[5,13,14,16]

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Gallstones. Gallstones (cholelithiasis) occur when mechanisms for the solubilisation of cholesterol or bilirubin fail or are overcome. They may be divided into those formed of pure cholesterol, which are usually solitary; pigment stones, largely made up of bilirubin or its derivatives; and mixed stones of cholesterol, bile pigment, and calcium salts, which form the great majority of cases seen in the West.

Gallstones are generally more common in women than in men. The prevalence also increases with age and obesity, although rapid weight loss as a result of dieting or surgery is associated with an increased risk.

As many as two-thirds of patients with gallstones are asymptomatic. Symptoms usually relate to the site of the stone although biliary colic is often present regardless of whether the stone is in the gallbladder or biliary tract. If the stone blocks the exit from the gallbladder, inflammation and bacterial infection may follow (acute cholecystitis), sometimes leading to perforation and subsequent peritonitis. Less commonly, obstruction of the common bile duct by gallstones (choledocholithiasis) may lead to cholestasis and jaundice; infection of the bile ducts and septicaemia may follow. Pancreatitis may also be associated with gallstone disease, and there may be an increased risk of developing malignant neoplasms of the gallbladder.

Treatment. Asymptomatic gallstones discovered during other investigations should not be treated, and even mildly symptomatic patients may be managed with analgesics and subsequent observation. Potent analgesics such as morphine may be needed in more severe cases (see Biliary and Renal Colic, p. 6.3). In symptomatic patients the preferred treatment for gallstones is surgical removal of the gallbladder by laparoscopic cholecystectomy which has largely replaced open surgery. Endoscopic retrograde cholangiopancreatography is also widely used to extract gallstones.

In patients unsuited to, or unwilling to undergo, surgery for gallbladder stones, drug therapy, alone or with lithotripsy, may be considered.

Exogenous bile acids have been tried in an attempt to dissolve the cholesterol component of gallstones. Ursodeoxycholic acid is more effective and is associated with fewer adverse effects than chenodeoxycholic acid. Combination therapy has also been tried but this is no more effective than ursodeoxycholic acid alone. Dissolution of gallstones is slow but can be achieved in about one-third of cases with the best results seen with small stones. However, about half of all successfully treated patients will develop further gallstones within 10 years. Studies of prophylactic bile acid therapy have mostly yielded disappointing results, although such therapy may be of benefit in patients on very-low-calorie diets, after surgery for weight loss, and in those receiving treatment with octreotide.

Somewhat larger stones may respond to extracorporeal shock-wave lithotripsy, mechanical lithotripsy, intracorporeal electrohydraulic lithotripsy, or fluoroscopically guided laser lithotripsy. Oral bile acids should then be given to dissolve the stone fragments.

Another method that has been used is the direct instillation of a solvent such as methyl *tert*-butyl ether or monoctanoin into the gallbladder, which dissolves stones in some patients. However, this form of treatment is no longer recommended given the frequency and seriousness of complications associated with the technique.

Patients with **stones in the common bile duct** or **acute cholecystitis** require prompt therapy because of the risk of serious complications; endoscopic sphincterotomy and physical retrieval of the stones with a basket or balloon catheter appears to be the preferred treatment, with open surgery as an alternative. A biliary stent to allow bile flow around the stone has been used as a temporary measure in patients with stones too large to remove by endoscopic sphincterotomy.

In patients who develop cholecystitis or cholangitis antibacterial therapy may be required (see Biliary-tract Infections, p. 174.2).

References.
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Adverse Effects and Precautions

Ursodeoxycholic acid may cause nausea, vomiting, and other gastrointestinal disturbances; diarrhoea is reported to occur less frequently than with chenodeoxycholic acid. Pruritus may occur. Calcification of gallstones and deterioration in liver function have been reported rarely.

Ursodeoxycholic acid should not be given to patients with intestinal and hepatic disorders that interfere with entero-hepatic circulation of bile salts (but see Chronic Liver Disease p. 2638.2). It is ineffective for the dissolution of calcified and radio-opaque gallstones and is of no value in patients without a patent and functioning gallbladder. Liver enzymes and bilirubin levels should be monitored every 4 weeks during the first 3 months of treatment and every 3 to 6 months thereafter. Licensed product information recommends that its use should be avoided in pregnancy.

References.
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Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ursodeoxycholic 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 06/10/11)

Interactions

Ursodeoxycholic acid should not be used with drugs that increase bile cholesterol such as oestrogenic hormones and cholesterol-lowering drugs such as clofibrate. Use with bile-acid binding drugs including antacids, charcoal, and colestyramine should be avoided since this may reduce the efficacy of therapy with ursodeoxycholic acid.

For references to the possible effects of ursodeoxycholic acid on ciclosporin, see p. 1955.1.

Pharmacokinetics

Ursodeoxycholic acid is absorbed from the gastrointestinal tract and undergoes enterohepatic recycling. It is partly conjugated in the liver before being excreted into the bile. Under the influence of intestinal bacteria the free and conjugated forms undergo 7α-dehydroxylation to lithocholic acid, some of which is excreted directly in the faeces and the rest absorbed and mainly conjugated and sulfated by the liver before excretion in the faeces. However, in comparison with chenodeoxycholic acid, less ursodeoxycholic acid undergoes such bacterial degradation.

References.
1. Crosignani A, *et al.* Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet* 1996; 30: 333–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Audecol; Dexo; Solutrat; UDCA; UR 03; Ursidesox; Ursofalk; Ursomax; Urzac; *Austral.*: Urso; Ursofalk; *Austria*: Ursofalk; *Belg.*: Ursochol; Ursofalk; *Braz.*: Ursacol; *Canad.*: Urso; *Chile*: Solvobil; Ursofalk; *China*: Taurolite (牆罗特); Ursofalk (优思弗); *Cz.*: Ursochol; Ursofalk; Ursosan; *Fin.*: Adursal; *Fr.*: Delursan; Ursolvan; *Ger.*: Cholit-Ursan†; Cholofalk†; UDC†; Ursochol; Ursofalk; *Gr.*: Ursofalk; *Hong Kong*: Urso; Ursofalk; Ursosan†; *Hung.*: Ursofalk; *India*: Actibile; Golbi; Intraliv-UD; Livokind; Udiliv; *Indon.*: Bstazor; Lofibra; Pramur†; Urdafalk; Urdahex; Ursochol; Ursolic; *Irl.*: Ursofalk; *Israel*: Ursofalk; Ursolit; *Ital.*: Biliepar; Desoxil; Deursil; Dissolursil; Praurs; Litoff; Liturso; Tauro; Tudcabil†; Urdes; Ursacol; Ursilon; Ursobil; Ursodamor†; Ursoflor; Ursolisin; *Jpn*: Urso; *Malaysia*: Ursofalk; *Mex.*: Ursofalk; *Neth.*: Ursochol; Ursofalk; *Norw.*: Ursofalk; *NZ*: Actigall; Ursofalk; *Philipp.*: Ursofalk; *Pol.*: Proursan; Ursocam; Ursofalk; Ursopol; *Port.*: Destolit; Ursofalk; *Rus.*: Urdoxa (Урдокса); Ursodex (Урсодекс); Ursofalk (Урсофальк); Ursoliv (Урсолив); Ursorom (Урсором); Ursosan (Урсосан); *S.Afr.*: Ursotan; *Singapore*: Ursofalk; *Spain*: Bilifalk; Ursobilane; Ursochol; *Swed.*: Ursofalk; Ursosan; *Switz.*: De-ursil; Ursochol; Ursofalk; *Thai.*: Udihep†; URSA; Ursofalk; Ursolin; *Turk.*: Taurolite; Ursofalk; *UK*: Destolit; Urdox; Ursofalk; Ursogal; *Ukr.*: Choludexan (Холудексан); Ursochol (Урсохол); Ursofalk (Урсофальк); Ursosan (Урсосан); *USA*: Actigall; Urso.

Multi-ingredient Preparations. *China*: Dages (达吉); *Ger.*: Lithofalk†; *Gr.*: Lithofalk; *Ital.*: Bilenor; *Jpn*: Cabe 2†; Eki Cabe S.

Pharmacopoeial Preparations

BP 2014: Ursodeoxycholic Acid Capsules; Ursodeoxycholic Acid Tablets;

USP 36: Ursodiol Capsules; Ursodiol Oral Suspension.

Urtica

Brännässleblad (nettle leaf); Brennessel; Dilgėlių lapai (nettle leaf); Kopřivový list (nettle leaf); Liść pokrzywy (nettle leaf); Nokkosenlehti (nettle leaf); Ortie; Ortie dioïque; Ortie, feuille d' (nettle leaf); Ortiga; Ortiga mayor; Pokrzywa zwyczajna; Stinging Nettle; Urtica dioica; Urticae folium (nettle leaf); Крапива Двудомная (*Urtica dioica*).

ATC Herb — HG04CW5009 (Urtica dioica: *herb*); *HA05AW5018* (Urtica dioica: *fruit*); *HG04CW5010* (Urtica dioica: *root*); *HA07XA5014* (Urtica dioica: *fruit*); *HG04BW5041* (Urtica dioica: *herb*); *HG04BW5042* (Urtica dioica: *root*); *HM02AX5005* (Urtica dioica: *fruit*); *HM01AW5024* (Urtica dioica: *herb*).

UNII — 710FLW4U46 (Urtica dioica); *1HN2NQ5OF9* (Urtica urens); *0DCW2P163M* (Urtica urens *leaf*).

Pharmacopoeias. In *Ger.* and *US* (both specify the root and rhizome of *Urtica dioica*).

Eur. (see p. vii) includes the leaf of *Urtica* spp. and also a form of *Urtica dioica* for homoeopathic preparations.

Br. includes a form of *Urtica urens* for homoeopathic preparations.

Ph. Eur. 8: (Nettle Leaf; Urticae Folium). The whole or cut dried leaves of *Urtica dioica*, *Urtica urens*, or a mixture of the 2 species. It contains a minimum of 0.3% for the sum of caffeoylmalic acid and chlorogenic acid expressed as

chlorogenic acid ($C_{16}H_{18}O_9$ = 354.3), calculated on the dried basis.

Ph. Eur. 8: (Common Stinging Nettle for Homoeopathic Preparations). The whole, fresh, flowering plant of *Urtica dioica*. Protect from light.

BP 2014: (Urtica Urens Herb for Homoeopathic Preparations). Fresh leaves and flowers of *Urtica urens*. The plant produces an itchy, burning sensation.

USP 36: (Stinging Nettle). The dried roots and rhizomes of *Urtica dioica* (Urticaceae), and may contain *Urtica urens*, known in commerce as dwarf nettle, as a minor component. It contains not less than 0.8% of total amino acids, not less than 0.05% of sitosterol, and not less than 0.003% scopoletin ($C_{10}H_8O_4$ = 192.2), calculated on the dried basis. Store in airtight containers. Protect from light.

Profile

Urtica (*Urtica dioica*) has been used in herbal medicine, mainly for urinary-tract and rheumatic disorders. *Urtica urens* has been used similarly.

Homoeopathy

Urtica has been used in homoeopathic medicines under the following names: Common stinging nettle; Urtica dioica; Urtica di.

Urtica urens has been used in homoeopathic medicines under the following names: Urtica ur; Urt. u.

References.

1. WHO. Radix Urticae. *WHO Monographs on Selected Medicinal Plants*, volume 2. Geneva: WHO, 2004. Also available at: http://apps.who.int/medicinedocs/en/d/Js4927e/31.html (accessed 04/02/10)
2. Safarinejad MR. *Urtica dioica* for treatment of benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled, crossover study. *J Herb Pharmacother* 2005; 5: 1–11.
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Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Uro-POS†; *Cz.*: Koprivovy Caj, Koprivova Nat; *Ger.*: Bazoton; Hox Alpha; Natu-lind; Natu-prosta; Prosta-Truw; Prostaforton†; Prostaherb N; Prostamed Urtica; Prostata†; Rheuma-Hek; Rheuma-Kapseln†; Selenk; Uro-POS†; Urol pros; Urtivit†; utk; *Pol.*: Prostaherb N; Urtix; *Rus.*: Prostaherb N (Простагерб Н); *Singapore*: Prostakan; *Switz.*: Valverde Prostate capsules; *UK*: DiaUrtica; Nettle Leaf Capsules; *Ukr.*: Allocholum (Аллохол).

Multi-ingredient Preparations. *Arg.*: Cistidac; Novo Prostasan; Prostafit; Troxac; *Austral.*: Bio Iron; Extralife Flow-Care†; Fe-Max; Haemo-Red; HRP; Irontona†; Prosta Balance; ProstaCo; Prostate Care; Prostate Health Formula; Vitatona†; *Austria*: Anaemodoron; Berggeist; Menodoron; Prostagutt; Urogutt; *Belg.*: Prostalane†; Prostatonin†; *Braz.*: Prostem Plus; *Canad.*: Floradix Kindervital†; Floradix Tab†; Rheuma Heilkrauter Tee†; Ultra Quercitin†; *Cz.*: Calmonal†; Diabeticka Cajova Smes-Megadiabetin†; Prostakan Forte; Pulmoran; Species Urologicae Planta; *Fr.*: Alpharegul Femme; Alpharegul Homme; Arthroflorine†; Biofirm; Cledist; Phytalgic; ProstaSecurA; Silibiol; Sun Vue; *Ger.*: Combudoron; Menodoron; Prostagutt forte; Vollmers praparierter gruner N; *Hong Kong*: Calmiderm; *Hung.*: Diabess; Herbalakt; Kilo-Nit; Majvedo es Detoxikalo; Prostatonin; Prostazyn; Telma; Urogin; Uroherb; Vensaxa; Vesevedo; Zeatax; *Irl.*: Combudoron†; *Ital.*: Bioestril Valeriana; Biothymus DS; Dren'it; Lignamid; Pluvio; Prostaplant; *Mex.*: Prosgutt; *Philipp.*: Lungcaire Plus; *Pol.*: Alliofil; Herbaton†; Immunofort; Naturapia Prostata†; Nefrobonisol; Seboren; Urofort; *Rus.*: Herbion Urtica (Гербион Уртика); Laxantis Species No 1 (Слабительный Сбор 1); Polygemostat (Полигемостат); Prostagutt Forte (Простагут Форте); *S.Afr.*: Combudoron†; Enzian Anaemodoron Drops†; Fragador†; Menodoron†; *Singapore*: Hair and Nails; *Switz.*: Combudoron; Kernosan 26; Menodoron; Prostagutt-F; Prostatonin; The d'avoine verte Vollmers†; Tisane Diuretique; Tisane pour les problemes de prostate; *UK*: Sinose; *Ukr.*: Fitoval Shampoo (Фитовал шампунь); Pravenor (Правенор); Prostaplant Forte (Простаплант Форте); Vitrum Beauty Elite (Витрум Бьюти Элит).

Homoeopathic Preparations. *Austral.*: Allergy Relief; *Austria*: Berberis Cosmoplex†; Sonnenbrandspray; *Canad.*: Common Mallow Combination†; Cutisitum†; Execalm†; Hives; Ursical Formula†; Urticalcin; *Chile*: Apis Compuesto; Arnica Compuesta; Bioactiv L; Similibus; *Cz.*: Galium; *Fr.*: Formica Rufa Compose; Rhus Toxicodendron Compose; Urocalm; Urtica Complexe No 82†; *Ger.*: Araniforce arthro; Chelidonium comp; Cysto Hevert; Heweurat N; Levisticum S; Phonix Solidago spag; Phonix Urtica-Arsenicum spag; Rheuma-Hevert†; Solidagosan N; *Neth.*: Actelite; Chavita 1; Combudoron; Itch Care; Phonix Solidago comp; Prrrikweg; Prurilite; Red Skin; Skin Care; Urtizon complex; *Rus.*: Urtica-Plus (Уртика-Плюс); *Switz.*: Silacten; Urticalcin; *UK*: Burns Cream; Combudoron; Fragador; Menodoron.

Usnea Barbata

Barba de capuchino; Barba de Fraile; Уснея Бородатая.
CAS — 125-46-2 (usnic acid).
UNII — D6DVA9TCAP.

NOTE. The name Barba de Fraile has also been used for *Fimbristylis littoralis*.

Profile

Usnea barbata is a lichen. It contains usnic acid, which is reported to have antimicrobial activity. *Usnea barbata* extract, usnic acid, and copper usnate have been used in topical preparations.

Adverse effects. Severe hepatotoxicity was believed to be associated with usnic acid contained in a multi-ingredient herbal preparation promoted for weight loss; one patient required emergency liver transplantation.[1] The toxicity of usnea barbata extracts and usnic acid has been reviewed.[2]

1. Sanchez W, *et al.* Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. *Mayo Clin Proc* 2006; 81: 541–4.
2. Guo L, *et al.* Review of usnic acid and Usnea barbata toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2008; 26: 317–38.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Vidermina; Zeta N†.

Multi-ingredient Preparations. *Indon.*: Scabicid; *Ital.*: Foot Zeta; Micofoot; Sideck Shampoo Antiforfora; Steril Zeta; Steril Zeta.

Homoeopathic Preparations. *Fr.*: Neurocynesine†; *Ger.*: Usnea-basan; *Neth.*: Neurocynesine†.

Valepotriates

Valepotriatos; Валепотриаты.

Acevaltrate *(rINN)*

Acévaltrate; Acevaltrato; Acevaltratum; Ацевалтрат.
4-Acetoxymethyl-(1 or 6)-3-(acetoxy-3-methylbutyryloxy)-1,6,7,7a-tetrahydro-(6 or 1)-isovaleryloxycyclopenta[c]pyran-7-spiro-2′-oxiran.
$C_{24}H_{32}O_{10}$=480.5
CAS — 25161-41-5.
UNII — S9MFK45GY9.

Didrovaltrate *(rINN)*

Didrovaltrato; Didrovaltratum; Дидровальтрат.
6-Acetoxy-1,4a,5,6,7,7a-hexahydro-1-isovaleryloxy-4-isovaleryloxymethylcyclopenta[c]pyran-7-spiro-2′-oxiran.
$C_{22}H_{32}O_8$=424.5
CAS — 18296-45-2.
UNII — KEN63D125F.

Valtrate *(pINN)*

Valtrato; Valtratum; Вальтрат.
4-Acetoxymethyl-1,6-di-isovaleryloxy-1,6,7,7a-tetrahydrocyclopenta[c]pyran-7-spiro-2′-oxiran.
$C_{22}H_{30}O_8$=422.5
CAS — 18296-44-1.
UNII — L3JQ035X9B.

Profile

Valepotriates are epoxy-iridoid esters, isolated from valerian (see below). They include acevaltrate, didrovaltrate, and valtrate. On prolonged storage and drying they are hydrolysed to yield isovaleric acid.

A mixture stated to contain acevaltrate, didrovaltrate, and valtrate has been used as a sedative and as an anxiolytic. Concern has been expressed over the potential toxicity of valepotriates which have been reported to have cytotoxic properties *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Valmane; *Gr.*: Valmane.

Multi-ingredient Preparations. *Arg.*: SDN 200.

Valerian

Baldrianwurzel; Korzeń kozłka; Kozlíkový kořen; Macskagyökér; Raíz de valeriana; Rizoma de valeriana; Valer; Valeriaananjuuri; Valerian Rhizome; Valerian Root; Valeriana; Valerianae Radix; Valerianarot; Valériane, racine de; Valerijonų šaknys; Валериана.
CAS — 8057-49-6 (valerian extract).
ATC — N05CM09.
ATC Vet — QN05CM09.
ATC Herb — HA03AW5061 (Valeriana officinalis: root, HN05CM5027 (Valeriana officinalis: root).
UNII — JWF5YAW3QW (Valeriana officinalis root).

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Eur.* also includes cut valerian root, valerian dry aqueous extract, dry hydroalcoholic extract, and tincture. *US.* includes the powdered form.

Jpn has Japanese Valerian from *V. fauriei*.

Ph. Eur. 8: (Valerian Root; Valerian BP 2014). The yellowish-grey to pale brownish-grey whole underground parts of *Valeriana officinalis*, including the rhizome surrounded by the roots and stolons, or by fragments of these parts. It contains not less than 0.4% v/w of essential oil for the whole drug and not less then 0.3% v/w for the cut drug, both calculated with reference to the dried drug. Protect from light.

USP 36: (Valerian). The subterranean parts of *Valeriana officinalis* (Valerianaceae), including the rhizome, roots, and stolons. It contains not less than 0.5% of volatile oil, not less than 0.05% of valerenic acid, and not less than 0.17% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid, on the dried basis. Store in airtight containers. Protect from light.

Uses and Administration

Valerian has sedative properties and is used as an extract, infusion, or tincture, or occasionally as the dried root, in preparations for anxiety states. It has also been used as a carminative. Valerian oil is used in aromatherapy. The odour of valerian may be removed from the skin and from hard surfaces with sodium bicarbonate.

References.

1. WHO. Radix Valerianae. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO, 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/29.html (accessed 04/02/10)
2. Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol* 1999; 51: 505–12.
3. Plushner SL. Valerian: valeriana officinalis. *Am J Health-Syst Pharm* 2000; 57: 328–35.
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6. Taibi DM, *et al.* A systematic review of valerian as a sleep aid: safe but not effective. *Sleep Med Rev* 2007; 11: 209–30.

Adverse Effects and Precautions

Chronic ingestion of valerian has been associated with headache, insomnia, agitation, and hepatotoxicity. Cardiac complications and delirium have been reported following abrupt withdrawal. Symptoms of overdose have included fatigue, lightheadedness, abdominal pain, tremor, hypotension, and mydriasis.

References.

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2. Garges HP, *et al.* Cardiac complications and delirium associated with valerian root withdrawal. *JAMA* 1998; 280: 1566–7.
3. Health Canada. Natural health products and adverse reactions: update. *Can Adverse React Newt* 2009; 19 (1): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n1-eng.pdf (accessed 16/08/10)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valerian 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 04/11/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nervisatis; *Austral.*: Dozile Natural; *Belg.*: Dormiplant Mono; Dormiplant†; Relaxine; Valerial; *Braz.*: Ansival; Noctaval; Recalm; Sonoripan; Sonotabs†; Traminer†; Valdorm; Valeriane; Valerimed; Valerin†; Valerix; Valezen; Valmane; *Canad.*: Nytol Natural Source; *Chile*: Sominex; *Cz.*: Kozlik; *Denm.*: Valerina Forte; *Fin.*: Dormiplant; Sedonium; *Ger.*: Baldorm†; Baldrivit; Baldurat†; Cefan†; Dolestan†; Euvegal Balance; Ivel mono†; Kytta-Sedativum†; Luvased mono†; Pascosedon Baldrian†; Sedonium; *India*: Naturbotic; *Irl.*: Valdrian; *Israel*: Relaxine; Valeton; *Ital.*: Noctaval; Ticalma; *Mex.*: Neolaikan; *Neth.*: Dormiplant; Nerviplant†; Sedonium†; Valdispert; *Norw.*: Sobal Forte†; Valerina Forte; *Pol.*: Cirkused; Relana Forte; Valerin; *Port.*: Livetan; Valdispert; Valditas†; *Rus.*: Cirkulin (Циркулин); Novo-Passit (Ново-Пассит); Phytorelax (Фиторелакс); Valdispert (Валдиспert); *S.Afr.*: Calmettes†; *Spain*: Ansiokey; Coenrelax; Normoval; Ratiomir†; Tauval†; Valdispert; Valeriana Orto†; Valsedan†; Verdeval†; *Swed.*: Baldrian-Dispert; Dormiplant; Neurol; Neval; Valerecen; Valerina; *Switz.*: Baldriparan pour la

nuit; Natu-Seda; Plantival Mono; ReDormin†; Sanadorm; Sedasol eco natura†; Sedonium; Valdispert†; *Thai.*: Valian-x; *Turk.*: Cirkulin Valerian; *UK*: DiaMood; DiaNight; DiaSleep; Kalms Night; Kira Restful Sleep; Niteherb; Phytorelax; Relaxisleep; Sedonium; SleepAid; SleepEezy; Valdrian; ValRelax; *Venez.*: Floral Pas.

Multi-ingredient Preparations. *Arg.*: Armonil; Calmtabs; Dioxicolagol; Incaico Serenidad; Nervocalm; Phytocalm; SDN 200; Sedanat†; Sedante Dia; Serenil; Sigmasedan; Valeriana Compuesta; Valeriana Diates†; Valeriana Oligoplex; Valeriana Relax Diates†; Valeriana; *Austral.*: Advanced Restless Leg Care; Calmo†; Coleus Complex†; Dan Shen Compound; Executive B†; Extralife Sleep-Care†; Humulus Compound; Lavandula Compound; Lemsip First Signs Cold & Flu Day + Night; Natural Deep Sleep†; Nervatona Focus; Nyal Cold + Flu Fighter Day + Night; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Nyal Sleep Aid; Passionflower Plus†; PM Dreamtime; ReDormin; Sleep Easy; Sleep Sound Formula; Valerian Complex; *Austria*: Baldracin; Baldrian comp; Hova; Nervenruh; Nerventee St Severin; Neurapas; Schlaf- und Beruhigungsdragees; Sedogelat; Wechseltee St Severin; *Belg.*: Calmiplant; Natudor; Seneuval; Songha†; *Braz.*: Remilev; Sedantol; Sominex; Sonhare; *Canad.*: Calm-Aid†; Calmane; Detente†; Dormane Plus; Dormane Tisane; Dormane; Herbal Insomnia†; Herbal Nerve†; Myoplex†; Nervinat; Nervrite; Painease; Phytocalm†; Relaxant; Relaxol; Salusan†; Sleep Relax; *Chile*: Armonyl Nocturno; Armonyl; Recalm†; Valupass; *Cz.*: Baldracin†; Doppelherz Energie-Tonikum†; Dr Theiss Schwedenbitter†; Euvekan†; Hova; Nervova Cajova Smes; Novo-Passit; Passit; Persen; Sanason†; Species Nervinae Planta; Valofyt Neo†; *Denm.*: Relana†; *Fr.*: Biocarde; Boribel Tisane No 8†; Calmiflorine†; Calmotisan†; Euphytose; Fibromyalgine Fort; Mediflor Tisane Calmante Troubles du Sommeil No 14; Neuroflorine†; Passinevryl†; Phytozac; Sedaloziâ†; Spasmine; Tranquital; *Ger.*: Alluna Nacht†; Allunapret; Ardeysedon; Avedorm duo†; Baldrian-Dispert Nacht†; Dr. Scheffler Bergischer Krautertee Nerven- und Beruhigungstee†; Dreierlei; Einschlaf-Kapsein extra†; Euvegal Entspannungs- und Einschlaftropfen; Euvegal; Heumann Beruhigungstee Tenerval; Hingfong-Essenz Hofmanns; Hyperesa†; Kneipp Gute Nacht†; Kytta-Sedativum; Moradorm S; Nervenkapseln; Neurapas; Oxacant-sedativ; Pascosedon; Phytonoctu; Plantival forte; Plantival novo; Psychotonin-sed†; Sandrin; Schwedentrunk Elixier; Seda-Plantina N; Sedacur; Sedariston Konzentrat†; Sedariston plus†; Sedaselect D; Selon; Tornix; Valeriana Beruhigungsdragees; Vivinox Day; *Gr.*: Passinevrol; Vivinox; *Hung.*: Cirkulin Valeriana; Doppelherz Energie Tonikum N; Euvekan†; Habstal-Nerv N; Hova; Kalms; Kardalept; ReDormin; Sedacur; Sedogelat; Worlshofener; *India*: Gynedol; Neo-Cordial; Nicy Days; *Indon.*: Slip-iZZZ†; *Irl.*: Avena Sativa Comp; Quiet Life; *Israel*: Calmanervin; Calmanervin; Nerven-Dragees; Passiflora Compound†; Passiflora; Redormin Night; Songha Night; *Ital.*: Anevrasi; Biocalm; Bioestril Valeriana; Calmason; Dormiplant; Pitosonno; Florelax; Glicero-Valerovit; Noctis; Parvisedil; Pineal Notte; Sedatol; Sedopuer F; *Mex.*: Ivel†; Nervinetas; Pasinordin; Plantival; *Neth.*: Plantival; *Norw.*: Euvekan†; Sobal†; Songha Natt; Valerina Natt; *Philipp.*: Sleepasil; *Pol.*: Calmina; Cardiol C; Cardiotonic; Cholitol; Doppelherz Energovital Tonik K; Doppelherz Energovital Tonik†; Dormiplant; Fortestomachicae; Guttae Stomachicae; Hova; Kalms; Krople Zoladkowe†; Krople Zoladkowe; Krople Zoladkowe; Lekosen†; Lumewal; Lunapret; Neocardina; Neospasmina; Neospasmol†; Nervendragees; Nervomag; Nervomix; Nervosan†; Nervosol; Nerwobonisol; Padma 28; Passispasmin; Passispasmol†; Persen; Prostapol; Relana†; Sedomix; Somnotent†; Tabletki Uspokajajace; Uroprost; Valiup†; Valuherb; Valused; *Port.*: Antispasmina Colica†; *Rus.*: Bromenval (Броменвал); Cardiovalen (Кардиовален); Dentaguttal (Дентагуттал); Dentaplus (Дентаплюс); Doppelherz Energotonik (Доппельгерц Энерготоник); Doppelherz Vitalotonik (Доппельгерц Виталотоник); Dormiplant (Дормиплант); Gastroguttal (Гастрогуттал); Herbion Drops for the Heart (Гербион Сердечные Капли)†; Insti (Инсти); Passifit (Пассифит); Persen (Персен); Sanason (Санасон); Sedativae Species No 2 (Седативный Сбор 2); Sedativae Species No 3 (Седативный Сбор 3); Valemidin (Валемидин); Valocormid (Валокормид); Zelenin (Зеленин); *S.Afr.*: Avena Sativa Comp†; Biral†; Entressdruppels HM; Helmontskruie†; Krampdruppels; Restin†; Stuidruppels; Wonderkroonessens; *Spain*: Dormiplant†; Melival; Nervikan; Netisum; Neurapas; Relana†; Sedonat; Tranquilgor; Valdispert Complex; Valeriana Leo; Valrelax†; *Swed.*: Dormeasan; Sedacur; *Switz.*: Arteria-vita; Baldriparan; Cardiophyt A; Dormeasan; Dormiplant; Dragees pour la detente nerveuse et le sommeil†; Dragees pour la detente nerveuse†; Dragees pour le coeur et les nerfs; Dragees sedatives Dr Welti; Femisan; Hova; Metabol; Nervinetten; Padma 28; Padmed Circosan; ReDormin; Relaxane; Relaxo; Songha Night; Strath Gouttes pour le nerfs et contre l'insomnie; Tisane calmante pour les enfants; Tisane pour le sommeil et les nerfs; Valverde Coeur; Valverde Detente dragees; Valverde Sommeil; Zeller Sommeil; *Turk.*: Nervikan; Nevrol Cemal; *UK*: Avena Sativa Comp; Bio-Strath Valerian Formula; Botanova; Chamomile Blend; Daily Tension & Strain Relief; DiaCalm; DiaDay & Night; DiaNight Plus; DiaRelax; DiaSleep Plus; Digestive; Dormeasan; Gerard House Serenity; Gerard House Somnus; Goodnight; Herbal Indigestion Naturtabs; Herbal Pain Relief; HRI Calm Life; HRI Golden Seal Digestive; HRI Night; Indigestion and Flatulence; Kalms Day; Kalms Sleep; Kalms; Laxative Tablets; Menopause Relief; Modern Herbals Stress; Natrasleep; Natural Herb Tablets; Neurotone; Newrelax; Niteherb Plus; Nodoff; Nytol Herbal; Padma 28; Padma Circosan; Period Pain Relief; PMT Formula; Prementaid; Puncto SleepTight; Quiet Days; Quiet Life; Quiet Nite; Quiet Tyme; Relax B*; Scullcap & Gentian Tablets; Sominex Herbal; Stressless; SuNerven; Sure-Lax (Herbal); Tranquil; Unwind Herbal Nytol; Valerian Passiflora and Hops; Valerina Day Time; Valerina Night-Time; Vegetable Cough Remover; Wellwoman; Wind & Dyspepsia Relief; *Ukr.*: Central-B (Централ-Б); Dormiplant (Дормиплант); Florised (Флорисед); Gastropin (Гастропин); Herbion Drops for Heart (Гербион Сердечные Капли)†; Herbion Sedative Drops (Гербион Успокаивающие Капли)†; Insti (Інсті); Menovalen (Меновален); Novo-Passit (Ново-Пассит); Persen (Персен); Relaxil (Релаксил); Sanason (Санасон)†; Sedafiton (Седафитон); Sedasen (Седасен); Sedavit (Седавит); Swedish Bitters Dr Theiss (Шведская Др Тайсс)†; Trivalumen (Тривалумен); Trypsidan (Трипсидан)†; *USA*: PowerSleep; *Venez.*: Equaliv; Euvekan; Femendol; Insocaps; Lupassin; Nervinetas; Pasidor; Pasifluidina; Rendetil; Sedival.

Homoeopathic Preparations. *Austral.*: Nervatona Focus; Sleep & Insomnia Relief; *Austria*: Aurumheel; Pasconal; Valerianaheel; *Canad.*: Amphosca†; Aurumheel†; Calsom†; Homeo-Form I†; Homeo-Form M†; Homeo-Form ST†; Insomnia Passiflora†; Insomnia; Kids Calm; Mental Alertness; Soludor†; Stress L72†; Stress; Travel Sickness; Valerianaheel Comp†; *Fr.*: Acidum Phosphoricum Complexe No 5; Amphosca Orchitine; Amphosca Ovarine; Boripharm No 3; Calmodren; Dolirelax†; L 72; Passiflora GHL; Poconeol no 32†; Soludor; Somnidoron; Strophantus Compose; Vespa Complexe No 46†; *Ger.*: Alho-Sedosan; Angioton S†; Avena sativa comp†; Calmvalera; Corselect N; Crataegus Herzcomplex; Diacard; Dormi-Gastreu S R14; Dormosyx; dysto-loges N; Hyperforat Nervo; Liquidorm N; Nervoid N; Nervoject F; Nervoregin comp; Neuro-Ginsan N; Pasconal Nerventropfen; Passiflora Complex†; Pectapas; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Rowo Rytesthin Ro-Plex (Rowo-318); Rytesthin; Sedacalman; Sedaphin†; Sedaselect; Sedativa-Injektopas; Tondinel H; Zappelin N; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Hung.*: Aurumheel; *Neth.*: Homeocare Nervo; Hyperilite; Weleda Avena Valeriana; *Rus.*: Valeriana-Plus (Валериана-Плюс); *Switz.*: Gouttes d'Or; Nelsons Nocturna†; *UK*: Noctura; *Ukr.*: Kindinorm (Киндинорм).

Pharmacopoeial Preparations

Ph. Eur.: Valerian Dry Hydroalcoholic Extract; Valerian Tincture; USP 36: Valerian Tablets; Valerian Tincture.

Valeric Acid

Acide pentanoïque; Ácido Valérico; Baldriansäure; Baldriānskābe; Kwas walerianowy; Kyselina Pentanová; Kyselina Valerová; Pentaanzuur; Pentanoic Acid; Pentansäure; Pentansyra; Propylacetic Acid; Valeriaanahappo; Valeriaanzuur; Valerianic Acid; Valeriansäure; Valeriánsav; Valeriansyra; *n*-Valeric Acid; Валериановая Кислота; Валерианова Киселина.

1-Butanecarboxylic acid.

$C_5H_{10}O_2$=102.1

CAS — 109-52-4.

UNII — GZK92PJM78.

NOTE. The name valeric acid has been used for a mixture of valeric acid and isovaleric acid.

Isovaleric Acid

Acide Isovalérianique; Ácido Isovalérico; Delphinic Acid; Isopentanoic Acid; Isopentansyra; Isopropylacetic Acid; Isovaleriaanzuur; Isovalerianic Acid; Isovaleriansäure; Isovaleriansyra; Kwas Izowalerianowy; 3-Methylbutaanzuur; 3-Methylbuttersäure.

3-Methylbutanoic acid.

$C_5H_{10}O_2$=102.1

CAS — 503-74-2.

UNII — 1BR7X184L5.

Profile

Valeric acid and isovaleric acid have been used in the treatment of nervous conditions. Some of their salts have been used similarly. Esters of valeric acid and isovaleric acid are used as flavourings and in perfumery.

Homoeopathy

Salts of valeric acid and isovaleric acid have been used in homoeopathic medicines. Zinc valerate has been used under the following names: zincum valerianicum; zincum isovalerianicum; zinkvalerianat; zinkisovalerianat

Preparations

Proprietary Preparations (details are given in Volume B)

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

Homoeopathic Preparations. *Austria*: Avena Rihom Komplex†; Globuli gegen Schlafstorungen; Nervoheel; Notta; *Canad.*: Ervopax†; *Fr.*: Cocculus Complexe No 73; Nervopax; Tarentula Complexe No 71; *Ger.*: Agnus castus comp†; Agnus femin; Alho-Sedosan; Calmvalera; Curare comp; Dormi-Gastreu S R14; Nervoregin comp; Neurexan; Presselin Nervenkomplex; Presselin Nervennahrung N†; Psychoneuroticum (Rowo-578)†; Psychoneuroticum N; Sedakatt; Zincum valerianicum comp; Zincum valerianicum-Hevert N†; *Hung.*: Nervoheel; *Neth.*: Kind 0-6 Kindival; Myamolite; Nervival; Nervoheel; *Rus.*: Notta (Нотта); Uspokoi (Успокой); Valeriana-Plus (Валериана-Плюс); *Switz.*: Nervoheel; *Ukr.*: Dormikind (Дормикинд); Notta (Нотта).

Valspodar *(BAN, USAN, rINN)*

PSC-833; SDZ-PSC-833; Valspodarum; Вальсподар.

Cyclo[[(2*S*,4*R*,6*E*)-4-methyl-2-(methylamino)-3-oxo-6-octenoyl]-L-valyl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl].

$C_{63}H_{111}N_{11}O_{12}$=1214.6

CAS — 121584-18-7.

UNII — Q7ZP55KF3X.

NOTE. The name Amdray has been used as a trade mark for valspodar.

Profile

Valspodar is an analogue of ciclosporin (p. 1945.2). It inhibits P-glycoprotein, which is associated with multidrug resistance. Valspodar is being investigated in various neoplasms to restore sensitivity of resistant tumour cells to anticancer drugs, but results have been disappointing.

Valspodar inhibits the cytochrome P450 isoenzyme CYP3A4, and may reduce the metabolism and clearance of other drugs.

References.

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Varenicline *(BAN, rINN)*

Vareniclene; Vareniclin; Vareniclina; Varénicline; Vareniclinum; Vareniklini; Vareniklin; Wareniklina; Вареиклин.

7,8,9,10-Tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline.

$C_{13}H_{13}N_3$=211.3

CAS — 249296-44-4.

ATC — N07BA03.

ATC Vet — QN07BA03.

UNII — W6HS99O8ZO.

Varenicline Tartrate *(BANM, USAN, rINNM)*

CP-526555-18; Tartrato de vareniclina; Vareniclina, tartrato de; Varénicline, Tartrate de; Vareniclini Tartras; Вареиклина Тартрат.

$C_{13}H_{13}N_3C_4H_6O_6$=361.4

CAS — 375815-87-5.

ATC — N07BA03.

ATC Vet — QN07BA03.

UNII — 82269ASB48.

Uses and Administration

Varenicline is a selective nicotinic receptor partial agonist that is used as an aid for smoking cessation.

Varenicline is given orally as the tartrate with doses expressed in terms of the equivalent amount of varenicline; 1.71 mg of varenicline tartrate is equivalent to about 1 mg of varenicline. An initial dose equivalent to 500 micrograms varenicline is given once daily for the first 3 days, increasing to 500 micrograms twice daily for the next 4 days. The dose from the eighth day for the remainder of the course is 1 mg

twice daily. The dose may be reduced to 500 micrograms twice daily if adverse effects are intolerable. Patients are advised to set a date to stop smoking and start varenicline 1 to 2 weeks before. Alternatively, the patient may stop smoking between 8 and 35 days after starting varenicline. Treatment is normally given for 12 weeks; in patients who successfully stop smoking, a further 12 weeks of treatment has been recommended to reduce the risk of relapse. In those who do not succeed in the first 12 weeks or who relapse after treatment, a second course of varenicline may be tried after factors contributing to the initial failure have been addressed. For doses in renal impairment, see below.

Reviews.
1. Zierler-Brown SL, Kyle JA. Oral varenicline for smoking cessation. *Ann Pharmacother* 2007; 41: 95–9.
2. Potts LA, Garwood CL. Varenicline: the newest agent for smoking cessation. *Am J Health-Syst Pharm* 2007; 64: 1381–4.
3. Hays JT, *et al.* Efficacy and safety of varenicline for smoking cessation. *Am J Med* 2008; 121 (suppl 1): S32–S42.
4. Anonymous. Varenicline for smoking cessation. *Drug Ther Bull* 2008; 46: 33–6.
5. Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med* 2008; 359: 2018–24.
6. Cahill K, *et al.* A preliminary benefit-risk assessment of varenicline in smoking cessation. *Drug Safety* 2009; 32: 119–35.
7. Jiménez-Ruiz C, *et al.* Varenicline: a novel pharmacotherapy for smoking cessation. *Drugs* 2009; 69: 1319–38.

Administration in renal impairment. In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) licensed product information for varenicline recommends a starting dose of 500 micrograms daily given orally, increased after 3 days to a maximum dose of 500 micrograms twice daily (in the USA) or 1 mg once daily (in the UK). In patients with end-stage renal disease undergoing haemodialysis, a maximum dose of 500 micrograms once daily may be given provided that this is well tolerated. No dosage adjustment is considered to be needed in patients with lesser degrees of impairment, although in patients with moderate renal impairment (creatinine clearance between 30 mL/minute and 50 mL/minute), dosing may be reduced to 1 mg daily in patients who have intolerable adverse effects. For reference to acute renal failure associated with varenicline in patients who had pre-existing moderate renal impairment, see Effects on the Kidneys, below.

Smoking cessation. Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist that is used as an aid for smoking cessation (p. 2570.2). Results from 2 randomised controlled studies[1,2] show greater efficacy than placebo as well as favourable results compared with bupropion, a standard treatment for smoking cessation. However, these studies also showed that nausea was reported in almost 30% of participants in the varenicline group; abnormal dreams were also a problem. A further 12 weeks of treatment with varenicline improved abstinence at 24 weeks in patients who stopped smoking in the first 12 weeks of treatment; after stopping all treatment, the reduced relapse rate was maintained in this group up to 28 weeks later (i.e. 1 year from the start of treatment).[3] Higher abstinence rates were achieved with varenicline than transdermal nicotine replacement therapy in a randomised open-label study.[4] Additionally, there was a greater reduction in craving, withdrawal, and smoking satisfaction at the end of varenicline therapy.

1. Gonzales D, *et al.* Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006; 296: 47–55.
2. Jorenby DE, *et al.* Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006; 296: 56–63. Correction. *ibid.*; 1355.
3. Tonstad S, *et al.* Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006; 296: 64–71.
4. Aubin H-J, *et al.* Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008; 63: 717–24.

Adverse Effects and Precautions

The most common adverse effect of varenicline is nausea; other adverse effects also commonly reported are headache, dizziness, somnolence, fatigue, sleep disturbances including abnormal dreams and insomnia, bad taste in the mouth, increased appetite, and gastrointestinal disturbances including vomiting, constipation, and flatulence. There have been reports of neuropsychiatric symptoms as well as exacerbation of pre-existing psychiatric illness in patients who have taken varenicline. Patients should be monitored for such symptoms, including suicidal ideation or behaviour, agitation, depression, or other changes in behaviour or thinking. Hypersensitivity reactions including angioedema have occurred, and severe cutaneous reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported rarely. Varenicline has been reported to be associated with a small increased risk of cardiovascular events in patients with pre-existing cardiovascular disease.

Varenicline should be given with caution to patients with renal impairment—see Effects on the Kidneys, below.

Dizziness, somnolence, loss of consciousness, and difficulty in concentrating have been reported, and patients should be warned to avoid potentially hazardous activities including driving or operating machinery.

Effects on the kidneys. Acute renal failure has been associated with varenicline in 2 men who had pre-existing moderate renal impairment;[1,2] acute interstitial nephritis was diagnosed in the second case.[2]

Licensed product information states that in patients with moderate renal impairment (creatinine clearance between 30 mL/minute and 50 mL/minute) varenicline exposure increased 1.5-fold compared with subjects with normal renal function, while in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) varenicline exposure increased 2.1-fold. Therefore reduction in dosage may be necessary when giving varenicline to patients with renal impairment—see Administration in Renal Impairment above for further details.

1. Bird ML, Vesta KS. Varenicline-associated acute renal failure. *Ann Pharmacother* 2008; 42: 1908–11.
2. Selby MG, *et al.* Does varenicline induce acute interstitial nephritis? *Mayo Clin Proc* 2009; 84: 560–1.

Effects on mental state. A retrospective cohort study[1] using data from the UK General Practice Research Database provided no clear evidence of an increased risk of self-harm, suicidal thoughts, or depression in patients given varenicline compared with other smoking cessation products, although it was acknowledged that the study power was limited and there may have been confounding factors not controlled for. Given the limitations of these data, it has been recommended that prescribers remain cautious when prescribing varenicline for smoking cessation.[2] A pooled analysis[3] of data from 10 randomised, double-blind, placebo-controlled studies found no significant increase in overall psychiatric disorders apart from disturbances in sleep; however, the subjects of this analysis were smokers with no current psychiatric problems and results from studies of varenicline in psychiatric patients are awaited.

1. Gunnell D, *et al.* Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. Abstract: *BMJ* 2009; 339: 1072. Full version: http://www.bmj.com/cgi/reprint/339/oct01_1/b3805 (accessed 01/07/10)
2. Lavigne JE. Smoking cessation agents and suicide. *BMJ* 2009; 339: 1042–3.
3. Tonstad S, *et al.* Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. *Drug Safety* 2010; 33: 289–301.

Effects on the skin. Varenicline has been temporally associated with development of maculopapular exanthema in a 71-year-old woman 7 days after she started treatment.[1] Varenicline was stopped and she was treated with diphenhydramine; all her symptoms gradually resolved over 8 days.

1. Song W, Miller WA. Diffuse exanthema in a patient receiving varenicline. *Am J Health-Syst Pharm* 2008; 65: 1239–41.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies varenicline 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

Varenicline is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 3 to 4 hours; bioavailability is high. Steady state concentrations are reached within 4 days of multiple oral dosing. Metabolism is minimal and about 92% of a dose is excreted unchanged in the urine; the elimination half-life is about 24 hours.

References.
1. Faessel HM, *et al.* Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *J Clin Pharmacol* 2006; 46: 991–8.
2. Burstein AH, *et al.* Pharmacokinetics, safety, and tolerability after single and multiple oral doses of varenicline in elderly smokers. *J Clin Pharmacol* 2006; 46: 1234–40.
3. Faessel HM, *et al.* Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. *J Clin Pharmacol* 2006; 46: 1439–48.
4. Ravva P, *et al.* Population pharmacokinetic analysis of varenicline in adult smokers. *Br J Clin Pharmacol* 2009; 68: 669–81.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Champix; *Austral.*: Champix; *Austria*: Champix; *Belg.*: Champix; *Braz.*: Champix; *Canad.*: Champix; *Chile*: Champix; *China*: Champix (伟沛); *Cz.*: Champix; *Denm.*: Champix; *Fr.*: Champix; *Ger.*: Champix; *Gr.*: Champix; *Hong Kong*: Champix; *Hung.*: Champix; *India*: Champix; *Indon.*: Champix; *Irl.*: Champix; *Israel*: Champix; *Ital.*: Champix; *Jpn*: Champix; *Malaysia*: Champix; *Mex.*: Champix; *Neth.*: Champix; *Norw.*: Champix; *NZ*: Champix; *Philipp.*: Champix; *Pol.*: Champix; *Port.*: Champix; *Rus.*: Champix (Чампикс); *Singapore*: Champix; *Spain*: Champix; *Swed.*: Champix; *Switz.*: Champix; *Thai.*: Champix; *Turk.*: Champix; *UK*: Champix; *Ukr.*: Champix (Чампикс); *USA*: Chantix.

Vascular Endothelial Growth Factor ⊗

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Profile

Vascular endothelial growth factor is a family of structurally related proteins involved in angiogenesis and vasculogenesis. VEGF-A, the first member of the family to be discovered and still often referred to as simply VEGF, is thought to provide most of the angiogenic effect of this family. Other members described to date include: VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.

A gene therapy product supplying the gene for vascular endothelial growth factor D via an adenoviral vector is under investigation for the prevention of stenosis in synthetic grafts used in haemodialysis.

Vasoactive Intestinal Peptide

Péptido vasoactivo intestinal; PIV; Vasoactive Intestinal Polypeptide; VIP; Вазоактивный Пептид Кишечника.

CAS — 37221-79-7.

Aviptadil *(BAN, rINN)*

Aviptadilum; Vasoactive Intestinal Octacosapeptide (Swine); Авиптадил.

$C_{147}H_{238}N_{44}O_{42}S$=3325.8

CAS — 40077-57-4.

UNII — A67JUW790C.

Profile

Vasoactive intestinal peptide acts as a hormone and neurotransmitter in various parts of the body; it is a potent relaxant of smooth muscle and has vasodilator and bronchodilator properties as well as stimulating the gastrointestinal tract to increased secretion. It is available as a synthetic analogue, aviptadil. It has been tried in the management of acute oesophageal food impaction, and for the treatment of acute respiratory distress syndrome, pulmonary arterial hypertension, acute lung injury, and chronic thromboembolic pulmonary hypertension. Aviptadil has been tried as a combination product with phentolamine for erectile dysfunction (p. 2348.2).

Vasoactive intestinal peptide has potential therapeutic applications in immunological disorders since it appears to inhibit inflammatory responses; it modulates the function of inflammatory cells via specific receptors affecting both innate and adaptive immunity.[1] It also appears to have endogenous neuroprotective properties within the CNS, possibly through influencing the expression and secretion of glial-cell derived neuroprotective factors. Consequently, it may have therapeutic potential in neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and stroke.[2]

1. Delgado M, *et al.* The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev* 2004; 56: 249–90.
2. Dejda A, *et al.* Neuroprotective potential of three neuropeptides PACAP, VIP and PHI. *Pharmacol Rep* 2005; 57: 307–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *NZ*: Invicorp.

Multi-ingredient Preparations. *Denm.*: Invicorp.

Vasopressin *(rINN/M)* ⊗

ADH; Antidiuretic Hormone; Beta-Hypophamine; Vasopressina; Vasopressini; Vasopressine; Vasopressinum; Vazopresin; Вазопрессин.

CAS — 11000-17-2 (vasopressin injection).

ATC — H01BA01.

ATC Vet — QH01BA01.

UNII — Y87Y826H08.

NOTE. Vasopressin Injection is *rINN*.

Pharmacopoeias. In *US*, which includes both argipressin and lypressin in this title.

An injection is included in *Jpn*.

USP 36: (Vasopressin). A polypeptide hormone having the properties of causing the contraction of vascular and other

smooth muscles, and of antidiuresis. It is prepared by synthesis. Store in airtight containers at 2 degrees to 8 degrees.

Argipressin *(BAN, rINN)* ⊗

Argipresina; Argipressine; Argipressinum; AVP; [8-Arginine]-vasopressin; Аргипрессин.
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2 cyclic (1→6) disulphide.
$C_{46}H_{66}N_{15}O_{12}S_2$=1084.2
CAS — 113-79-1.
ATC — H01BA06.
ATC Vet — QH01BA06.
UNII — Y4907O6MFD.

Description. Argipressin is a form of vasopressin obtained from most mammals including man but excluding pig. It is usually prepared synthetically. Lypressin (see below) is vasopressin from pig.

Argipressin Tannate *(BANM, USAN, rINNM)* ⊗

8-L-Arginine-vasopressin Tannate; Argipressine, Tannate d'; Argipressini Tannatum; CH107; Tanato de argipresina; Аргипрессина Таннат.
Tannins compound with argipressin.
ATC — H01BA06.
ATC Vet — QH01BA06.

Units

8.2 units of argipressin for bioassay are contained in about 20 micrograms of synthetic peptide acetate (with human albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Lypressin *(BAN, USAN, rINN)* ⊗

L-8; Lipresina; Lipressina; Lipresszin; LVP; Lypressilin; Lypressine; Lypressinum; Липрессин.
[8-Lysine]vasopressin; Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2 cyclic (1→6) disulphide.
$C_{46}H_{65}N_{13}O_{12}S_2$=1056.2
CAS — 50-57-7.
ATC — H01BA03.
ATC Vet — QH01BA03.
UNII — 7CZF3L922Y.

Description. Lypressin is the form of vasopressin present in the posterior pituitary of pigs.

Pharmacopoeias. *US* includes Lypressin Nasal Solution.

Incompatibility. Vasopressin was shown to be physically compatible (when injected at the Y-site in an intravenous tubing set) when tested in intravenous fluids with other drugs commonly used in cardiac arrest.[1] However, tests of vasopressin with drugs commonly used in septic shock showed physical incompatibility with phenytoin (when mixed in infusion bags).[2] Precipitation has also been reported[3] with vasopressin and furosemide together in intravenous fluids (tested at the Y-site).

1. Feddema S, *et al.* Physical compatibility of vasopressin with medications commonly used in cardiac arrest. *Am J Health-Syst Pharm* 2003; 60: 1271–2.
2. Barker B, *et al.* Visual compatibility of vasopressin with other injectable drugs. *Am J Health-Syst Pharm* 2005; 62: 1969, 1975–6.
3. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; 63: 906–8.

Units

7.7 units of lypressin are contained in about 23.4 micrograms of synthetic peptide (with albumin 5 mg and citric acid) in one ampoule of the first International Standard (1978).

Uses and Administration

Vasopressin is 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. Vasopressin has a direct antidiuretic action on the kidney, increasing tubular reabsorption of water. It also constricts peripheral blood vessels and causes contraction of the smooth muscle of the intestine, gallbladder, and urinary bladder. It has practically no oxytocic activity.

Vasopressin, which is usually given parenterally or intranasally in the synthetic forms of argipressin or lypressin, is used in the treatment of cranial diabetes insipidus due to a deficiency in antidiuretic hormone. It is ineffective in nephrogenic diabetes insipidus. Argipressin has also been used in the prevention and treatment of postoperative abdominal distension, and was formerly given to remove gas in abdominal visualisation procedures. Argipressin or lypressin are used in the treatment of bleeding oesophageal varices. Argipressin may have a role in cardiopulmonary resuscitation and shock due to vasodilatation.

In the treatment of cranial diabetes insipidus to control polyuria, argipressin may be given subcutaneously or intramuscularly; the dose in the UK is 5 to 20 units every 4 hours. In the USA, 5 to 10 units given 2 to 4 times daily has been used. Alternatively, argipressin or lypressin has been given as a nasal spray; dosage should be individually adjusted as required. A long-acting oily suspension of vasopressin tannate was formerly used by intramuscular injection in diabetes insipidus.

In the initial control of variceal bleeding argipressin is given in an initial dose of 20 units in 100 mL of glucose 5% infused intravenously over 15 minutes. Lypressin has also been given for bleeding oesophageal varices. Doses for children are given under Administration in Children, below.

Vasopressin has also been used as a vasoconstrictor in local anaesthetic injections.

Administration. Results[1] suggesting that although intravenous argipressin produced much higher plasma concentrations than intranasal, the latter evoked a greater CNS response.

1. Pietrowsky R, *et al.* Brain potential changes after intranasal vs intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. *Biol Psychiatry* 1996; 39: 332–40.

Administration in children. Although not licensed in the UK for use in children, the *BNFC* includes a dose of argipressin for adjunctive treatment of acute massive haemorrhage of the gastrointestinal tract or oesophageal varices in patients aged from 1 month to 18 years. An initial dose of 0.3 units/kg (up to 20 units) is given intravenously over 20 to 30 minutes, followed by a continuous infusion of 0.3 units/kg per hour adjusted according to response to a maximum of 1 unit/kg per hour. If the bleeding stops the infusion is continued at the same dose for 12 hours, then gradually withdrawn over 24 to 48 hours; the maximum duration of treatment should be 72 hours.

Vasopressin given by continuous intravenous infusion in an average dose of 9 milliunits/kg per hour was safe and effective in 5 children who had diabetes insipidus as a manifestation of severe brain injury.[1] A dose of 1.5 to 3 milliunits/kg per hour has also been used safely for postoperative diabetes insipidus in 2 children aged 3 years and under.[2] Similar initial doses of argipressin were used in 3 comatose children with cranial diabetes insipidus,[3] while a published algorithm for the management of acute cranial diabetes insipidus has recommended an initial dose of vasopressin of 0.25 to 1 milliunits/kg per hour, subsequently titrated to achieve an appropriate output and specific gravity of urine, and a serum sodium value of between 140 and 145 mmol/litre.[4]

1. Ralston C, Butt W. Continuous vasopressin replacement in diabetes insipidus. *Arch Dis Child* 1990; 65: 896–7.
2. McDonald JA, *et al.* Treatment of the young child with postoperative central diabetes insipidus. *Am J Dis Child* 1989; 143: 201–4.
3. Lee Y-J, *et al.* Continuous infusion of vasopressin in comatose children with neurogenic diabetes insipidus. *J Pediatr Endocrinol Metab* 1995; 8: 257–62.
4. Lugo N, *et al.* Diagnosis and management algorithm of acute onset of central diabetes insipidus in critically ill children. *J Pediatr Endocrinol Metab* 1997; 10: 633–9.

Advanced cardiac life support. Vasopressin (as argipressin) may be used as an alternative to adrenaline in cardiopulmonary resuscitation (see Cardiac Arrest, p. 1268.3). In a preliminary study argipressin 40 units by intravenous injection appeared to be of value in the treatment of cardiac arrest due to ventricular fibrillation.[1] Spontaneous circulation returned in 16 of 20 patients so treated; 14 were successfully resuscitated on arrival in hospital and 8 survived to be discharged. In comparison, of 20 patients treated with 1 mg of adrenaline intravenously only 7 were resuscitated and 3 survived till discharge. However, a larger study[2] found no difference between vasopressin and adrenaline in the rates of survival to hospital admission for patients with ventricular fibrillation or pulseless electrical activity, although vasopressin was associated with a higher rate of hospital admission and discharge among patients with asystole. It also found that two doses of vasopressin followed by a single dose of adrenaline resulted in a better survival rate than three doses of adrenaline. Another large study[3] of patients who had a cardiac arrest while in hospital and were treated with either vasopressin 40 units or adrenaline 1 mg, found no difference in survival to discharge from hospital. A systematic review[4] of 5 studies, including these 3, found no clear advantage for the use of vasopressin over adrenaline in the treatment of cardiac arrest. Further studies using a combination of vasopressin and adrenaline have had mixed results. No improvement in outcome was found when both vasopressin and adrenaline were used in out-of-hospital cardiac arrest,[5] but an in-hospital study[6] using vasopressin, adrenaline, and corticosteroids found that survival was improved.

1. Lindner KH, *et al.* Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997; 349: 535–7.
2. Wenzel V, *et al.* A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; 350: 105–13.
3. Stiell IG, *et al.* Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet* 2001; 358: 105–9.
4. Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med* 2005; 165: 17–24.
5. Gueugniaud P-Y, *et al.* Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008; 359: 21–30.
6. Mentzelopoulos SD, *et al.* Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009; 169: 15–24.

Diabetes insipidus. For a discussion of diabetes insipidus and its management, including reference to the use of vasopressin analogues (particularly desmopressin), see p. 2348.2.

Haemorrhagic disorders. There are reports of vasopressin being used in the management of various haemorrhagic disorders including blood loss in abortion and caesarean section[1,2] and haemoptysis.[3,4] Infusion of vasopressin into the superior or inferior mesenteric artery has been used in the management of lower gastrointestinal bleeding, but modern embolisation techniques may be associated with fewer complications.[5] For the use of vasopressin in upper gastrointestinal variceal haemorrhage, see below.

1. Schulz KF, *et al.* Vasopressin reduces blood loss from second-trimester dilatation and evacuation abortion. *Lancet* 1985; ii: 353–6.
2. Lurie S, *et al.* Subendometrial vasopressin to control intractable placental bleeding. *Lancet* 1997; 349: 698.
3. Noseworthy TW, Anderson BJ. Massive hemoptysis. *Can Med Assoc J* 1986; 135: 1097–9.
4. Bilton D, *et al.* Life threatening haemoptysis in cystic fibrosis: an alternative therapeutic approach. *Thorax* 1990; 45: 975–6. Correction. *ibid.* 1991; 46: 274.
5. Darcy M. Treatment of lower gastrointestinal bleeding: vasopressin infusion versus embolization. *J Vasc Interv Radiol* 2003; 14: 535–43.

Nocturnal enuresis. For references to the use of the vasopressin analogue, desmopressin, in nocturnal enuresis, see p. 2356.1.

Shock. Argipressin has been reported to have beneficial vasopressor effects in the management of shock (p. 1279.3) due to vasodilatation. It has been given by continuous intravenous infusion at a dose of about 2 to 6 units/hour as supplemental therapy in patients who could not be adequately managed with conventional vasopressor therapy.[1,2] In a retrospective study[3] vasopressin given with or without catecholamines for haemodynamic support of shock did not increase the incidence of venous thromboembolism compared with catecholamines given alone. Further reports[4,5] of the benefit of vasopressin in septic shock suggest that it may be of value in reducing doses of catecholamine vasopressors.

1. Dünser MW, *et al.* Management of vasodilatory shock: defining the role of arginine vasopressin. *Drugs* 2003; 63: 237–56.
2. Dünser MW, *et al.* Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003; 107: 2313–19.
3. Doepker BA, *et al.* Thromboembolic events during continuous vasopressin infusions: a retrospective evaluation. *Ann Pharmacother* 2007; 41: 1383–9.
4. Obritsch MD, *et al.* Effects of continuous vasopressin infusion in patients with septic shock. *Ann Pharmacother* 2004; 38: 1117–22.
5. Szumita PM, *et al.* Vasopressin for vasopressor-dependent septic shock. *Am J Health-Syst Pharm* 2005; 62: 1931–6.

Variceal haemorrhage. Vasopressin has been widely used to control bleeding from oesophageal varices, as discussed under Monoethanolamine, on p. 2563.1. However, terlipressin, and more recently octreotide, have been found to have some advantages over vasopressin, including bolus dosage and fewer adverse effects, and octreotide is increasingly preferred for this purpose. Glyceryl trinitrate has been given with the aim of counteracting the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure.[1-4]

1. Stump DL, Hardin TC. The use of vasopressin in the treatment of upper gastrointestinal haemorrhage. *Drugs* 1990; 39: 38–53.
2. Williams SGJ, Westaby D. Management of variceal haemorrhage. *BMJ* 1994; 308: 1213–17.
3. Sung JJY. Non-surgical treatment of variceal haemorrhage. *Br J Hosp Med* 1997; 57: 162–6.
4. McCormack G, McCormack PA. A practical guide to the management of oesophageal varices. *Drugs* 1999; 57: 327–35.

Adverse Effects

Large parenteral doses of vasopressin may give rise to marked pallor, pounding headache, vertigo, sweating, tremor, nausea, vomiting, diarrhoea, eructation, cramp, and a desire to defaecate; some of these effects may also occur after large intranasal doses of lypressin. In women, vasopressin may cause uterine cramps of a menstrual character. Hyponatraemia with water retention and signs of water intoxication can occur.

Hypersensitivity reactions have occurred and include urticaria and bronchoconstriction. Anaphylactic shock and cardiac arrest have been reported.

Vasopressin may constrict coronary arteries. Chest pain, myocardial ischaemia, and infarction have occurred following injection, and fatalities have been reported. Other cardiovascular effects include occasional reports of arrhythmias and bradycardia, as well as hypertension. Peripheral vasoconstriction has resulted in gangrene, and thrombosis as well as local irritation at the injection site may occur.

Nasal congestion, irritation, and ulceration have been reported occasionally after intranasal use, usually as lypressin; systemic effects at usual intranasal doses are mostly reported to be mild.

Effects on the heart. Arrhythmias, including ventricular tachycardia and fibrillation,[1] torsade de pointes,[2-4] and asystole[5] are among the adverse effects of vasopressin. Paradoxical bradycardia and hypotension have also been reported.[6]

1. Kelly KJ, *et al.* Vasopressin provocation of ventricular dysrhythmia. *Ann Intern Med* 1980; 92: 205–6.
2. Eden E, *et al.* Ventricular arrhythmia induced by vasopressin: torsade de pointes related to vasopressin-induced bradycardia. *Mt Sinai J Med* 1983; 50: 49–51.
3. Stein LB, *et al.* Fatal torsade de pointes occurring in a patient receiving intravenous vasopressin and nitroglycerin. *J Clin Gastroenterol* 1992; 15: 171–4.
4. Paigel DO, *et al.* Torsade de pointes complicating the treatment of bleeding esophageal varices: association with neuroleptics, vasopressin, and electrolyte imbalance. *Am J Gastroenterol* 1995; 90: 822–4.
5. Fitz JD. Vasopressin induction of ventricular ectopy. *Arch Intern Med* 1982; 142: 644.
6. Kraft W, *et al.* Paradoxical hypotension and bradycardia after intravenous arginine vasopressin. *J Clin Pharmacol* 1998; 38: 283–6.

Ischaemia. Myocardial ischaemia and infarction have occurred with vasopressin but there have also been reports of non-cardiac ischaemia and infarction.[1-10]

1. Greenwald RA, *et al.* Local gangrene: a complication of peripheral Pitressin therapy for bleeding esophageal varices. *Gastroenterology* 1978; 74: 744–6.
2. Colombani P. Upper extremity gangrene secondary to superior mesenteric artery infusion of vasopressin. *Dig Dis Sci* 1982; 27: 367–9.
3. Lambert M, *et al.* Reversible ischemic colitis after intravenous vasopressin therapy. *JAMA* 1982; 247: 666–7.
4. Anderson JR, Johnston GW. Development of cutaneous gangrene during continuous peripheral infusion of vasopressin. *BMJ* 1983; 287: 1657–8.
5. Reddy KR, *et al.* Bilateral nipple necrosis after intravenous vasopressin therapy. *Arch Intern Med* 1984; 144: 835–6.
6. Brearly S, *et al.* A lethal complication of peripheral vein vasopressin infusion. *Hepatogastroenterology* 1985; 32: 224–5.
7. Sweren BS, Bohlman ME. Gastric and splenic infarction: a complication of intraarterial vasopressin infusion. *Cardiovasc Intervent Radiol* 1989; 12: 207–9.
8. Maceyko RF, *et al.* Vasopressin-associated cutaneous infarcts, alopecia, and neuropathy. *J Am Acad Dermatol* 1994; 31: 111–13.
9. Lin RY, *et al.* Vasopressin-induced amber-like skin necrosis. *Dermatology* 1997; 195: 271–3.
10. Dunser MW, *et al.* Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003; 31: 1394–8.

Treatment of Adverse Effects

The antidiuretic effects on water retention and sodium imbalance may be treated by water restriction and a temporary withdrawal of vasopressin. Severe cases may require osmotic diuresis alone or with furosemide.

Extravasation. Localised intravenous and intra-arterial guanethidine was used in the treatment of a patient with extravasation of vasopressin.[1] The intra-arterial use of guanethidine was considered to have helped to avoid necrotic changes.

1. Crocker MC. Intravascular guanethidine in the treatment of extravasated vasopressin. *N Engl J Med* 1981; 304: 1430.

Precautions

Vasopressin should not be used in patients with chronic nephritis with nitrogen retention. It should be avoided or given only with extreme care, and in small doses, to patients with vascular disease, especially of the coronary arteries.

It should be given with care to patients with conditions which might be aggravated by water retention including asthma, epilepsy, migraine, and heart failure. Fluid intake should be adjusted to avoid hyponatraemia and water intoxication. Care is also required in hypertension or other conditions that may be exacerbated by a rise in blood pressure. Nasal absorption of vasopressin may be impaired in patients with rhinitis.

Abuse. Vasopressin or its analogues have been abused as so-called 'smart drugs' for their supposed effect on memory recall and cognition.

Resistance. Antibodies to vasopressin were detected in 6 of 28 patients being treated for diabetes insipidus, all of whom had a decrease in antidiuretic effect with previously effective argipressin or lypressin therapy;[1] desmopressin and chlorpropamide remained effective in these patients. There have been reports of patients with diabetes insipidus of pregnancy unresponsive to argipressin but responsive to desmopressin.[2] This was probably due to excessive placental production of vasopressinase, an enzyme which degrades argipressin.

1. Vokes TJ, *et al.* Antibodies to vasopressin in patients with diabetes insipidus: implications for diagnosis and therapy. *Ann Intern Med* 1988; 108: 190–5.
2. Shah SV, Thakur V. Vasopressinase and diabetes insipidus of pregnancy. *Ann Intern Med* 1988; 109: 435–6.

Interactions

The antidiuretic effects of vasopressins might be expected to be enhanced in some patients receiving chlorpropamide, clofibrate, carbamazepine, fludrocortisone, urea, or tricyclic antidepressants. Lithium, heparin, demeclocycline, noradrenaline, and alcohol may decrease the antidiuretic effect. Ganglion-blocking drugs may increase sensitivity to the pressor effects of vasopressins.

Cimetidine. A report of severe bradycardia and heart block leading to asystole in a patient given combined vasopressin and cimetidine therapy.[1]

1. Nikolic G, Singh JB. Cimetidine, vasopressin and chronotropic incompetence. *Med J Aust* 1982; 2: 435–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Novopressina-V; *Austral.*: Pitressin; *Braz.*: Encrise; *Canad.*: Pressyn; *Gr.*: Pitressin; *India*: CPressin; *Irl.*: Pitressin; *NZ*: Pitressin; *UK*: Pitressin†; *USA*: Pitressin Synthetic.

Multi-ingredient Preparations.

Used as an adjunct in:. *Gr.*: Neo-Lidocaton.

Pharmacopoeial Preparations
USP 36: Lypressin Nasal Solution; Vasopressin Injection.

Veratrine

Veratriini; Veratrin; Veratrina; Veratrinum.
CAS — 8051-02-3 (veratrine mixture); 71-62-5 (veratrine amorphous); 62-59-9 (veratrine crystallised, cevadine).

Description. Veratrine is a mixture of alkaloids from the dried ripe seeds of *Schoenocaulon officinale* (Melanthiaceae) (see p. 2611.2). Veratrine should be distinguished from protoveratrines obtained from *Veratrum* spp.

Uses and Administration

Veratrine should not be used internally. It was formerly applied externally for its analgesic properties and as a parasiticide, especially for head lice, but even when used in this way there is danger of systemic poisoning from absorption.

Adverse Effects, Treatment, and Precautions

Veratrine resembles aconite (p. 2428.3) in its action on the peripheral nerve endings and poisoning should be treated similarly. It is an intense local irritant and has a powerful direct stimulating action on all muscle tissues. It has a violent irritant action on mucous membranes, even in minute doses, and must be handled with great care. When ingested it causes violent vomiting, purging, an intense burning sensation in the mouth and throat, and general muscular weakness.

Veratrol

Catechol Dimethyl Ether; *O*-Dimethoxybenzene; 2-Methoxyanisole; Pyrocatechol Dimethyl Ether; Veratrole.
1,2-Dimethoxybenzene.
$C_8H_{10}O_2$=138.2
CAS — 91-16-7.
UNII — 61WJZ2Q41L

Profile

Veratrol is a phenolic compound that has been used topically in preparations for musculoskeletal, skin, and mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Bain de Bouche Lipha†; Synthol.

Green Veratrum

American Hellebore; American Veratrum; Ballestera Verde; Eléboro verde; Green Hellebore; Green Hellebore Rhizome; Veratro americano; Veratro Verde; Veratrum Viride; Чемерица зелёная.
CAS — 65072-04-0.
ATC — C02KA01.
ATC Vet — QC02KA01.
ATC Herb — HC02KA5002 (Veratrum viride: rhizome).
UNII — 36K54AW5KX (Veratrum viride); 19783Q7T5Q (Veratrum viride root).

Description. Green veratrum consists of the dried rhizome and roots of *Veratrum viride* (Liliaceae) from which are derived the alkaloidal mixtures alkavervir and cryptenamine.

White Veratrum

Ballestera Blanca; Eléboro blanco; Eléboro europeo; European Hellebore; Vedegambre; Veratrum Album; White Hellebore; White Hellebore Rhizome; Чемерица белая.
ATC — C02KA01.
ATC Vet — QC02KA01.
ATC Herb — HC02KA5001 (Veratrum album: rhizome).
UNII — 7DEL4FSK0E (Veratrum album); QNS6W5US1Z (Veratrum album root).

Description. White veratrum consists of the dried rhizome and roots of *Veratrum album* (Liliaceae) from which are derived the alkaloids protoveratrine A and B.

Uses and Administration

White and green veratrum contain several pharmacologically active alkaloids that produce centrally mediated peripheral vasodilatation and bradycardia. They have been used in the treatment of hypertension but are generally considered to produce an unacceptably high incidence of adverse effects and have largely been replaced by less toxic antihypertensives.

Both green and white veratrum have also been used as insecticides.

Homoeopathy

White Veratrum has been used in homoeopathic medicines under the following names: Veratrum album; Veratrum alb; Ver. alb.

Green Veratrum has been used in homoeopathic medicines under the following names: Veratrum viride; Veratrum vir.

Adverse Effects

Veratrum alkaloids may cause nausea and vomiting at conventional therapeutic doses. Other adverse effects include epigastric and substernal burning, sweating, mental confusion, bradycardia or cardiac arrhythmias, dizziness, and hiccup. Profound hypotension and respiratory depression can occur at high doses.

References.

1. Schep LJ, *et al.* *Veratrum* poisoning. *Toxicol Rev* 2006; 25: 73–8.

Sneezing powder. Various symptoms of intoxication occurred in 7 patients due to the use of a sneezing powder containing white veratrum alkaloids.[1]

1. Fogh A, *et al.* Veratrum alkaloids in sneezing-powder: a potential danger. *J Toxicol Clin Toxicol* 1983; 20: 175–9.

Treatment of Adverse Effects

Activated charcoal may be considered within 1 hour of ingestion. Symptomatic bradycardia or cardiac arrhythmias can be treated with atropine. The patient should be placed in a supine position with the feet raised; more severe hypotension may require the use of inotropes such as dopamine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Neth.*: Diarrheel S.

Homoeopathic Preparations. *Austral.*: Vitatona Energy†; *Austria*: Daram; Metavirulent; Pertudoron†; Rytmopasc; Veratrum Med Complex; *Canad.*: Pertudoron 1†; *Cz.*: Hepeel; Spascupreel S†; *Fr.*: Abbe Chaupitre no 19†; Apomorphinum Complexe No 97†; Drosera Complexe No 64; Geranium Complexe No 108†; Pertudoron; Vinicard†; *Ger.*: Arnica Oligoplex; Corvipas SL; Entero-Gastreu S R4; HanoCor N; Infi-Camphora; Infi-Echinacea; Infihepan; metavirulent; Myonasan; Pertudoron 1; Rytmopasc; Viscum album H†; *Hung.*: Hepeel; Spascupreel; *Neth.*: Collite; Entero-Gastreu R4; Homeocare Digesto; Kind 0-6 Kindigest; Okugest; *Rus.*: Avia-Mor (Авиа-Мор); Tonginal (Тонгинал); *S.Afr.*: Pertudoron Drops†; *Switz.*: Diarrheel S; Hepeel; metavirulent; Regenaplex Nr. 21c; Regenaplex Nr. 31a; *Ukr.*: Gastrokind (Гастрокинд); Tonginal (Тонгинал).

Verbascum

Aaron's Rod (*Verbascum thapsus*); Bouillon Blanc; Bouillon blanc, fleur de (mullein flower); Divizmovy květ (mullein flower); Great Mullein (*Verbascum thapsus*); Kungsljusblomma (mullein flower); Mullein; Okorfarkkoro virág (mullein flower); Orange Mullein (*Verbascum phlomoides*); Tubitž žiedai (mullein flower); Ukontulikukankukka (mullein flower); Verbasci flos (mullein flower); Wollblumen; Коровяк Обыкновенный (*Verbascum thapsus*).

ATC Herb — HR05WA5063 (Verbascum densiflorum flower); UNII — C9TDZ7U172 (Verbascum thapsus); CZ1843G1J8 (Verbascum phlomoides flower).

NOTE. The name Aaron's Rod has been applied to several plants including *V. densiflorum*, *Solidago* spp., and *Sempervivum tectorum*.

Pharmacopoeias. *Eur.* (see p. vii) includes the dried flowers.

Ph. Eur. 8: (Mullein Flower; Verbasci flos). The dried flowers, reduced to the corolla and the androecium, of *Verbascum thapsus*, *V. densiflorum*, and *V. phlomoides*. Store in airtight containers.

Profile

Verbascum flower is an ingredient of herbal remedies for cough and cold symptoms. The dried leaves and stems have also been used.

References.

1. Turker AU, Gurel E. Common mullein (*Verbascum thapsus* L.): recent advances in research. *Phytother Res* 2005; 19: 733–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Noverban.

Multi-ingredient Preparations. *Austral.*: ResCo; *Austria*: Brust- und Hustentee St Severin; Pervivo; *Canad.*: Echinamide Cold and Cough†; Honey Blend Herbal Cough Syrup; *Cz.*: Species Pectorales Planta; *Fr.*: Pectoflorine†; *Ger.*: Equisil N†; *Hung.*: Antipoll; Bittner; *Mex.*: Bronkitose Mielimon; *Philipp.*: Lungcaire Plus; *Pol.*: Flegatussin†; Gwajatussin; Pervivo; Termasil; *Rus.*: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера).

Homoeopathic Preparations. *Austria*: Globuli gegen Heiserkeit; Metasinusit; *Fr.*: Aesculus Complexe No 103; *Ger.*: Dolo-Injektopas; Hewallergia Complex; Neuralgie-Gastreu R70; Pulmo Bronchialcomplex; *Switz.*: metasinusit; Regenaplex Nr. 71b.

Verbenone

Werbenon; Вербенон.

2-Pinen-4-one; 4,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-one.

$C_{10}H_{14}O$=150.2

CAS — 80-57-9 (verbenone); 18309-32-5 (d-verbenone); 1196-01-6 (l-verbenone).

ATC Vet — QR05CA11 (l-verbenone).

UNII — 99S17893UW (d-verbenone); IFV46DXC6U (dl-verbenone).

Profile

Verbenone is a terpene found in lemon-verbena oil, rosemary oil (p. 2607.3) and some other essential oils. It has been used, sometimes with pine oil, for respiratory disorders.

Verbenone has also been used as an insect repellent in forestry.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Ozopulmin G†; Ozopulmin.

Multi-ingredient Preparations. *Ital.*: Ozopulmin G; Ozopulmin G; Ozopulmin.

Vervain

Herba Columbariae; Herba Verbenae; Shop Vervain Wort; Verbena; Verveine Officinale; Вербена Лекарственная (*Verbena officinalis*).

ATC Herb — HN05CM5028 (Verbena officinalis: herb); HR05YA5029 (Verbena officinalis: herb); HG02WD5001 (Verbena officinalis: herb); HA01WD5001 (Verbena officinalis: herb).

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

Ph. Eur. 8: (Verbena Herb). The whole or fragmented, dried aerial parts of *Verbena officinalis* collected during flowering. It contains a minimum of 15% of verbenalin ($C_{17}H_{24}O_{10}$=388.4) calculated with reference to the dried drug.

Profile

Vervain, the aerial parts of *Verbena officinalis* (Verbenaceae), has been used for many disorders. It is a bitter and has been used for digestive disorders. It also has sedative properties and has been used for anxiety disorders and as a tonic during convalescence from chronic illness.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Avena Complex†; Calmo†; Herbal Rest & Relax; Sinupret; *Austria*: Sinupret; *Canad.*: Calmane; *Cz.*: Sinupret; *Fr.*: Aromadigest†; Aromazen†; Santane A4†; Tisane Provencale no 4†; Vigilia†; *Ger.*: Sinupret; *Hong Kong*: Sinupret; *Hung.*: Antipoll; Sinupret; *Indon.*: Sinupret†; *Ital.*: Neoderma 47; *Malaysia*: Sinupret; *Mex.*: Bisolsinus; *Philipp.*: Sinupret; *Pol.*: Sinupret; *Rus.*: Sinupret (Синупрет); *Singapore*: Sinupret; *Swed.*: Sinova; *Switz.*: Sinupret; Tisane pour nourissons et enfants; *Thai.*: Sinupret†; *UK*: Athera; Goodnight; HRI Night; Kalms Sleep; Modern Herbals Menopause; Modern Herbals Stress; Napiers Herbal Stress & Sleep Aid; Newrelax; Period Pain Relief; Prementaid; Scullcap & Gentian Tablets; Sinueeze; Sinuherb; Stressless; SuNerven; *Ukr.*: Sinupret (Синупрет).

Homoeopathic Preparations. *Fr.*: Poconeol no 48; *Ger.*: Phonix Thuja-Lachesis spag.

Vetrabutine Hydrochloride *(BANM, rINNM)*

Dimophebumine Hydrochloride; Hidrocloruro de vetrabutina; Sp-281; Vetrabutina, hidrocloruro de; Vétrabutine, Chlorhydrate de; Vetrabutini Hydrochloridum; Ветрабутина Гидрохлорид.

N,N-Dimethyl-α-(3-phenylpropyl)veratrylamine hydrochloride.

$C_{20}H_{27}NO_2$,HCl=349.9

CAS — 3735-45-3 (vetrabutine); 5974-09-4 (vetrabutine hydrochloride).

Profile

Vetrabutine hydrochloride is used as a uterine relaxant in veterinary medicine.

Vinburnine *(rINN)*

CH-846; 3α,16α-Eburnamonine; (-)-Eburnamonine; Vinburnina; Vinburninum; Vincamone; Винбурнин.

(3α,16α)-Eburnamenin-14(15*H*)-one.

$C_{19}H_{22}N_2O$=294.4

CAS — 4880-88-0.

ATC — C04AX17.

ATC Vet — QC04AX17.

UNII — G54D0HMY25.

Profile

Vinburnine is an alkaloid related to vincamine (below) and has been used in conditions associated with cerebral circulatory insufficiency.

Vinburnine phosphate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Cervoxan; *Port.*: Cervoxan; *Spain*: Cervoxan.

Vincamine *(BAN, rINN)*

Vincamina; Vincaminum; Винкамин.

Methyl (3α,16α)-14,15-dihydro-14β-hydroxyeburnamenine-14-carboxylate.

$C_{21}H_{26}N_2O_3$=354.4

CAS — 1617-90-9.

ATC — C04AX07.

ATC Vet — QC04AX07.

UNII — 996XVD0JHT.

Pharmacopoeias. In *Fr.*

Profile

Vincamine is an alkaloid obtained from *Vinca minor* (Apocynaceae). It is claimed to increase cerebral circulation and utilisation of oxygen and has been used in a variety of cerebral disorders. Vincamine may have adverse effects on the cardiovascular system and care should be taken in patients with hypertension or cardiac dysfunction.

Vincamine salts including vincamine hydrochloride, oxoglurate, teprosilate, and hydrogen tartrate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vinkhum; *China*: Ao Bo Lan (奥勃兰); *Gr.*: Etuamol; Livenza; Neuro-Kranit; Sozinalin; Vencano; Verolinex; Vincaminor; *Ital.*: Vinca-Treis; *Mex.*: Vincapan; *Port.*: Arteriovinca; Cervinca; *Spain*: Tefavinca; Vincacen†; *Switz.*: Oxygeron†; *Ukr.*: Oxybral (Оксибрал); Vinoxin (Винокси).

Multi-ingredient Preparations. *Arg.*: Ribex; *Fr.*: Rheobral†; *Mon.*: Vincarutine; *Port.*: Anacervix; *Spain*: Anacervix; Devincal†.

Homoeopathic Preparations. *Hung.*: Naso-Heel S.

Vinpocetine *(BAN, USAN, rINN)*

Apovincaminato de etilo; AY-27255; Ethyl Apovincaminate; Ethyl Apovincaminoate; RGH-4405; Vinpocetin; Vinpocetina; Vinpocétine; Vinpocetinum; Vinposetiini; Винпоцетин.

Ethyl (3α,16α)-eburnamenine-14-carboxylate.

$C_{22}H_{26}N_2O_2$=350.5

CAS — 42971-09-5.

ATC — N06BX18.

ATC Vet — QN06BX18.

UNII — 543512OBTC.

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

Ph. Eur. 8: (Vinpocetine). A white or slightly yellow, crystalline powder. Practically insoluble in water; soluble in dichloromethane; slightly soluble in anhydrous alcohol.

USP 36: (Vinpocetine). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Vinpocetine is a derivative of vincamine (above) that has been given orally in cerebrovascular disorders and dementia. Good evidence to support its use in cognitive impairment is lacking.

References.

1. Grandt R, *et al.* Vinpocetine pharmacokinetics in elderly subjects. *Arzneimittelforschung* 1989; 39: 1599–1602.
2. Blaha L, *et al.* Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome. *Hum Psychopharmacol Clin Exp* 1989; 4: 103–11.
3. Berecziki D, Fekete I. A systematic review of vinpocetine therapy in acute ischaemic stroke. *Eur J Clin Pharmacol* 1999; 55: 349–52.
4. Szatmári SZ, Whitehouse P. Vinpocetine for cognitive impairment and dementia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 31/03/06).
5. Kemény V, *et al.* Acute and chronic effects of vinpocetine on cerebral hemodynamics and neuropsychological performance in multi-infarct patients. *J Clin Pharmacol* 2005; 45: 1048–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Vicog; *China*: Bai Rui De (百锐得); Bang Chuan Nai Xin (邦川乃新); Bo Jian (博健); Cavinton (开文通); Chang Gui Qing (长贵青); Ding Na (丁那); Duolikang (多力康); Hua Mai Tong (华迈通); Jie Li Shu (杰力纾); Li Nuo Sheng (丽诺生); LiHuan (立环); Ning Xu Xin (宁绪欣); Qing He (青禾); Run He Er (润海尔); Run Tan (润坦); Shu Lin (松霖); Tailiping (泰力平); Tong Ming (同铭); Wei Li Ming (维力明); Yi Qi Xian (易齐先); Yuan Tuo (元妥); Zui Xing (最醒); *Cz.*: Cavinton; Vicebrol; *Hung.*: Cavinton; *India*: Neurovin; *Pol.*: Cavinton; Vicebrol; Vinpoton; *Port.*: Cavinton; DC Vin†; Ultra-Vinca; Vipocem; *Rus.*: Bravintone (Бравинтон); Cavinton (Кавинтон); Telectol (Телектол); Vincetin (Винцетин)†; Vinpoton (Винпотон)†; *Singapore*: Cavinton; *Thai.*: Cavinton; Vinpocen; Vinpotin; *Ukr.*: Cavinton (Кавинтон).

Multi-ingredient Preparations. *Rus.*: Vinpotropile (Винпотропил).

Vinyl Chloride

Cloruro de vinilo; VCM; Vinilo, cloruro de; Vinyl Chloride Monomer; Winylu chlorek.

Chloroethylene.

C_2H_3Cl=62.50

CAS — 75-01-4.

UNII — WD06X94M2D.

Profile

Vinyl chloride is used in the manufacture of polyvinyl chloride (PVC) and other vinyl polymers. Occupational exposure to vinyl chloride in polymerisation plants has been associated with acro-osteolysis, especially in the terminal phalanges of the fingers, a condition resembling Raynaud's phenomenon, and sclerodermatous skin changes. Liver damage and hepatic angiosarcoma, splenomegaly, thrombocytopenia, impaired respiratory function, and chromosomal abnormalities have also occurred.

References.

1. Infante PF, *et al.* Genetic risks of vinyl chloride. *Lancet* 1976; i: 734–5.
2. Black CM, *et al.* Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. *Lancet* 1983; i: 53–5.

3. Piratsu R, *et al.* La mortalità dei produttori di cloruro di vinile in Italia. *Med Lav* 1991; **82**: 388–423.
4. Riordan SM, *et al.* Vinyl chloride related hepatic angiosarcoma in a polyvinyl chloride autoclave cleaner in Australia. *Med J Aust* 1991; **155**: 125–8.
5. Mur JM, *et al.* Spontaneous abortion and exposure to vinyl chloride. *Lancet* 1992; **339**: 127–8.
6. McLaughlin JK, Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. *J Epidemiol Biostat* 1999; **4**: 253–75.
7. Bolt HM. Vinyl chloride—a classical industrial toxicant of new interest. *Crit Rev Toxicol* 2005; **35**: 307–23.
8. Sherman M. Vinyl chloride and the liver. *J Hepatol* 2009; **51**: 1074–81.

Visnadine *(BAN, rINN)*

Visnadina; Visnadinum; Виснадин.

10-Acetoxy-9,10-dihydro-8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[2,3-*f*]chromen-9-yl 2-methylbutyrate.

$C_{21}H_{24}O_7$=388.4

CAS — 477-32-7.

ATC — C04AX24.

ATC Vet — QC04AX24.

UNII — 0RL4V0K263.

Profile

Visnadine is a vasodilator obtained from *Ammi visnaga* fruit (p. 2441.2) or by synthesis. It has been used in coronary, cerebral, and peripheral vascular disorders.

Volatile Mustard Oil

Allylsenföl; Essence of Mustard; Mostaza, aceite esencial de; Oleum Sinapis Volatile; Эфирное Горчичное Масло.

ATC Herb — HM02AW5002 (Brassica nigra: *essential oil*).

Profile

Volatile mustard oil, prepared from black mustard seeds (p. 2566.1), is largely composed of allyl isothiocyanate (p. 2436.3). It is an extremely powerful irritant that has been used as a counter-irritant and rubefacient. Expressed mustard oil contains a smaller proportion of volatile oil and has been used as a less powerful counter-irritant.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Allviol; Benegel; Gelflex; Nevrol†; *Canad.*: External Anti-Pain Oil†; Penetrating Rub†; *Cz.*: Apisarthron†; *Rus.*: Apisarthron (Апизартрон); Efcamon (Эфкамон); *Spain*: Dolokey†; *Switz.*: DUL-X warm; Knobel Huile N†; *UK*: Nine Rubbing Oils; Radian-B Red Oils; Red Oil; *USA*: Dermolin; Musterole Extra.

Black Walnut

American Black Walnut; Black Walnut Nut; Carya; Nogal Americano; Nogal Negro; Nogueira-preta; Noyer Noir; Noyer Noir d'Amérique; Noyer Noir d'Amérique du Nord; Schwarze Walnuss; Schwarznuss; Schwarznuss Baum.

UNII — 02WM57RXZJ (black walnut); J7DAA933PR (black walnut extract); 3M3MMX2NG2 (black walnut bark); I2OQ2W1NI2 (black walnut leaves).

NOTE. The name Black Walnut has also been applied to the English Walnut, *Juglans regia* (see below). Some sources do not distinguish between Black Walnut and English Walnut. The name Walnut may refer to either species, and other common names for English Walnut have also been applied (erroneously) to Black Walnut.

Distinguish from Butternut (White Walnut), p. 2463.2.

Profile

The fruit hulls and other parts of the black walnut, *Juglans nigra* (*Wallia nigra*), Juglandaceae, are sometimes used in herbal medicine, although the English walnut (see below) is more commonly used. Black walnut has been used in the traditional medicine of some North American native tribes.

The fruit is used as a foodstuff and the tree is a source of brown dye.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Wormwood Complex.

English Walnut

Carpathian Walnut; Common Walnut; Echte Walnuss; Hetaoren (seed); Hu Tao; Hu Tao Ren (seed); Juglandis Folium (leaf); Madeira Walnut; Nogal; Nogal Común; Nogal Europeo; Nogal Inglés; Nogueira-comum; Noyer Commun; Noyer Royal; Persian Walnut; Semen Juglandis (seed); Vainōt; Walnussblätter (leaf).

ATC Herb — HD03WA5005 (Juglans regia: *leaf*); *HD10AW5001* (Juglans regia: *leaf*).

UNII — 1V3SHR7Q87 (Juglans regia *nut*); *3BA2N709NG* (Juglans regia *flowering top*); *8SHKB87105* (Juglans regia *leaf*).

NOTE. The name Black Walnut has been applied to the English Walnut, *Juglans regia*, but is more commonly used for *J. nigra* (see above). Some sources do not distinguish between Black Walnut and English Walnut. The name Walnut may refer to either species, and other common names for English Walnut have also been applied (erroneously) to Black Walnut.

The name Juglans is applied to both English Walnut and Butternut (see p. 2463.2).

Pharmacopoeias. In *Chin.* and *Fr.*

Profile

Various parts of the English walnut, *Juglans regia* (*J. duclouxiana*; *J. fallax*; *J. kamaonica*; *J. kamaonia*; *J. orientis*; *J. sinensis*) (Juglandaceae), are used in herbal medicine preparations.

The leaf is used for gastrointestinal disorders. The leaf is also used externally for superficial inflammation and as an antiperspirant.

The hull of the fruit (pericarp) has traditionally been used in preparations for a variety of conditions including disorders of the gastrointestinal tract and skin.

Unspecified parts are used in preparations for constipation and other gastrointestinal disorders and for disorders of the upper respiratory tract.

Walnut kernels are used in traditional Chinese medicine.

The kernel is used as a foodstuff and has been promoted as having a beneficial effect on blood lipids when included in the diet.

Homoeopathy

English walnut has been used in homoeopathic medicines under the following names: Juglans regia; Juglans reg.

The flowers of *Juglans regia* are also used in homoeopathic medicines under the following names: Juglans regia, flos; Juglans reg, flos.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Juglanex (Юглянэкс).

Multi-ingredient Preparations. *Cz.*: Original Schwedenbitter; *Ger.*: Imupret; *Hung.*: Gombarex; *Rus.*: Tonsilgon N (Тонзилгон Н); *Ukr.*: Imupret (Имупрет); Tonsilgon N (Тонзилгон)†.

Homoeopathic Preparations. *Austria*: Lymphomyosot; *Canad.*: Itires; Minerals+; Rexorubia†; *Cz.*: Lymphomyosot; *Fr.*: Diacure; Hepatodrainol; Poconeol no 37; Rexorubia; Uranium Compose†; *Ger.*: Haut-Gastreu R60; Lymphomyosot; Regenaplex Haut G; Tumoglin†; *Hung.*: Lymphomyosot; Pro-Aller; PSY-Stabil; *Neth.*: Acidolite; Hepatodrainol†; Lymfelite; *Port.*: Hepatodrainol; *Ukr.*: Lymphomyosot (Лімфомиозот).

Water

Acqua; Agua; Agua potable; Aqua; Aqua Communis; Aqua Fontana; Aqua Potabilis; Eau Potable; Vand; Vann; Vatten; Vesi; Víz; Wasser; Woda; Вода.

H_2O=18.02

CAS — 7732-18-5.

Purified Water

Agua purificada; Aqua Purificata; Eau purifiée; Išgrynintas vanduo; Puhdistettu vesi; Tisztított víz; Vatten, renat; Voda čištěná; Woda oczyszczona; Очищенная Вода (purified water); Дистиллированная Вода (distilled water).

UNII — 059QF0K00R.

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

Eur. also includes Highly Purified Water. *US* also includes Sterile Purified Water.

Some pharmacopoeias only include distilled water or have additional monographs for demineralised water or distilled water.

Ph. Eur. 8: (Water, Purified; Aqua Purificata). It is water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised. It is prepared from suitable potable water either by distillation, by ion exchange, by reverse osmosis, or by any other suitable method. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Sub-monographs cover Purified Water in Bulk and Purified Water in Containers.

Ph. Eur. 8: (Water, Highly Purified; Aqua Valde Purificata) It is water intended for the preparation of medicinal products where water of high biological quality is needed except where Water for Injections is required.

USP 36: (Purified Water). It is prepared from potable water by a suitable process.

Preparation. *DEIONISATION.* By passing potable water through columns of anionic and cationic ion-exchange resins, ionisable substances can be removed, producing a water of high specific resistance. Colloidal and non-ionisable impurities such as pyrogens may not be removed by this process.

DISTILLATION. In this process water is separated as vapour from non-volatile impurities and is subsequently condensed. In practice, non-volatile impurities may be carried into the distillate by entrainment unless a suitable baffle is fitted to the still.

Water for Injections

Agua para Inyecciones; Agua para Inyectables; Aq. pro Inj.; Aqua ad iniectabilia; Aqua ad Injectionem; Aqua Injectabilis; Aqua pro Iniectione; Aqua pro Injectione; Aqua pro Injectionibus; Eau pour préparations injectables; Injekcinis vanduo; Injektionesteisiin käytettävä vesi; Vatten för injektionsvätskor; Víz parenterális célra; Voda na injekci; Wasser für Injektionszwecke; Water for Injection; Woda do wstrzykiwań; Вода Для Инъекций.

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

US also includes Sterile Water for Injection, Sterile Water for Inhalation, Sterile Water for Irrigation, and Bacteriostatic Water for Injection.

Ph. Eur. 8: (Water for Injections). It is water for the preparation of medicines for parenteral administration when water is used as the vehicle, and for dissolving or diluting substances or preparations for parenteral administration. It is prepared by distillation of potable water or purified water from a neutral glass, quartz, or suitable metal still fitted with an effective device for preventing the entrainment of droplets; the first portion of the distillate is discarded and the remainder collected. Store in conditions designed to prevent growth of micro-organisms and to avoid any other contamination. Sub-monographs cover Water for Injections in Bulk and Sterilised Water for Injections.

USP 36: (Water for Injection). It is purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and micro-organisms. When used for the preparation of parenteral solutions it should be sterilised first or the final preparation should be sterilised after preparation. Sterile Water for Injection, Inhalation, or Irrigation and Bacteriostatic Water for Injection are the subjects of separate monographs.

Profile

There are international standards for the quality of water intended for human consumption. Toxic substances such as arsenic, barium, cadmium, chromium, copper, cyanide, lead, and selenium may constitute a danger to health if present in drinking water in excess of the recommended concentrations. Water-borne infections are also a hazard.

Fluoride is regarded as an essential constituent of drinking water but may endanger health if present in excess—see Sodium Fluoride, p. 2090.1. Ingestion of water containing large quantities of nitrates may cause methaemoglobinaemia in infants; many countries have standards for nitrates in water.

The use of tap water containing metal ions (such as aluminium, copper, and lead), fluoride, or tosylchloramide sodium, for dialysis may be hazardous.

Hard water contains soluble calcium and magnesium salts, which form scale and sludge in boilers, water pipes, and autoclaves; they also cause the precipitation of soap and prevent its lathering. Temporary hardness in water is due to the presence of bicarbonates which are converted to insoluble carbonates on heating. Permanent hardness is due to dissolved chlorides, nitrates, and sulfates, which do not form a precipitate on heating. The presence or absence of such salts can play a part in cardiovascular health.

Without further purification, potable water may be unsuitable for certain pharmaceutical purposes. In such instances, purified water should always be used. Most pharmacopoeias include monographs on various preparations of water, such as water suitable for injections. Potable water should not be used when such preparations of water are specified.

Excessive ingestion of water can lead to water intoxication with disturbances of the electrolyte balance.

References.

1. Manz F, *et al.* The most essential nutrient: defining the adequate intake of water. *J Pediatr* 2002; **141**: 587–92.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Humaqua; Rins-Aqua; *Turk.*: Ser-Piz; *UK*: Aquasol; Uriflex W; *USA*: Fleet Bagenema.

Multi-ingredient Preparations. *Philipp.*: BioSil†.

Homoeopathic Preparations. *Fr.*: Urarthone.

Pharmacopoeial Preparations
BPC 1973: Surgical Chlorinated Soda Solution;
USP 36: Cascara Sagrada Fluidextract.

Wheat

Blé; Froment; Frumento; Grano; Trigo; Weizen; Пшеница Мягкая.
UNII — 4J2I0SN84Y.

NOTE. Distinguish from Triticum, a synonym for Couch-grass (see p. 2487.2).

Profile

Wheat (*Triticum* spp., Poaceae) is a grass cultivated worldwide as a cereal crop. Common wheat (*Triticum aestivum*, (*T. vulgare*)) is the source of wheat germ and wheat-germ oil (below). Malted grain of wheat is used in the preparation of malt extract (p. 2080.2). Wheat is also used as a source of bran (p. 1823.3) and starch (p. 2095.1).

Wheat germ is used in preparations for lesions of the skin and mucous membranes and as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Dermocrem†; Vagitrene; *Canad.*: Dermatix Fitocream†; *Ger.*: Vulnostimulin; *Hong Kong*: Benefiber; *India*: Benefiber; *Ital.*: Fitostimoline; Step 2; *Singapore*: Benefiber; *Turk.*: Fito; *USA*: Benefiber; *Venez.*: Derain; Gynoderain.

Multi-ingredient Preparations. *Arg.*: Amenite Plus; Cicatul; Microlift; *Canad.*: Floradix Kindervital†; *Cz.*: Revalid; *Hung.*: Revalid; *Ital.*: Decon Ovuli; Fitostimoline; Sclerovis H Plus; Solecin†; *Mex.*: Fitoestimulina; Italdermol; *Port.*: Fitocreme; *Singapore*: Pro-4; *Spain*: Dextricea†; *Switz.*: Revalid†; *UK*: S.P. H.P.; *Ukr.*: Revalid (Ревалид); *Venez.*: Multivit Natura.

Homoeopathic Preparations. *UK*: Fragador.

Wheat-germ Oil

Búzacsíraolaj; Germes de blé, huile de; Huile de Germe de Blé; Kviečių gemalų aliejus; Oleum Tritici Germinis; Pšeničný olej; Tritici aestivi oleum; Tritici Oleum; Vehnänalkioöljy; Vetegroddolja; Масло Пшеничных Зародышей.
CAS — 8006-95-9.
ATC Herb — HA11YA5001 (Triticum aestivum: *germ oil*).
UNII — 14C97E680P.

Pharmacopoeias. *Eur.* (see p. vii) includes Wheat-germ Oil, Refined, and Wheat-germ Oil, Virgin.

Ph. Eur. 8: (Wheat-germ Oil, Refined; Tritici Aestivi Oleum Raffinatum). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or by other suitable mechanical means and/or by extraction. It is then refined. A suitable antioxidant may be added. A clear, light yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40 degrees to 60 degrees. Relative density about 0.925. Store in an airtight container. Protect from light.

Ph. Eur. 8: (Wheat-germ Oil, Virgin; Tritici Aestivi Oleum Virginale). The fatty oil obtained from the germ of the grain of *Triticum aestivum* by cold expression or other suitable mechanical means. A clear, light yellow or golden-yellow liquid. Practically insoluble in water and in alcohol; miscible with light petroleum at 40 degrees to 60 degrees. Relative density about 0.925. Store in an airtight container. Protect from light.

Profile

Wheat-germ oil is a rich source of vitamin E (p. 2119.1). It is included in dietary supplements and in preparations for lesions of the skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Tre-en-en; Vitamin E Complex; *Braz.*: Gamaline-V; Primoris†; *Canad.*: Salusan†; *Fr.*: Actymine†; Bio-Selenium†; Omegaline Solaire; Phytophanere†; *Hung.*: Aktivit; *India*: Climdan; E-Cod Omega; E-Cod Plus; Evaren; Evox; Hartivit; Humidus; Korisma; Lycogold; Lycostar-CM; Marc Free; Moiste; *Indon.*: Eviprostat; *Ital.*: Babigoz Crema Protettiva; Babysteril; Eavit Plus; Eavit; Eu-Visus; Granvit; Ottovis; Vitalux; *Jpn*: Eviprostat; *Pol.*: Klosterfrau Aktiv; *Port.*: Rilastil Dermo Solar; *Rus.*: Vitamax (Витамакс)†; *Singapore*: Eviprostat; *Switz.*: Priorin N; *Turk.*: Priorin; *UK*: No-Sor Nose Balm; Skin Perfecting Oil; *Ukr.*: Energin (Энергин); Gold Ray (Голд Рей); Reytoil (Рейтоил).

Wild Carrot

Dauci Herba; Daucus; Queen Anne's Lace; Zanahoria silvestre; Морковь Дикая.

NOTE. The name Queen Anne's lace has also been used for cow parsley (*Anthriscus sylvestris*), another umbellifer. The name Wild Carrot has also been applied to Hemlock, p. 2524.3.

Pharmacopoeias. In *Chin.*

Profile

The fruits of the wild carrot, *Daucus carota* (Umbelliferae) have been used as a diuretic and anthelmintic, and are included in herbal preparations for various indications. Other parts of the plant have been used in folk medicine. Carrot seed oil is used in aromatherapy. The root of the cultivated form, *D. carota* subsp. *sativus*, is a culinary item and a source of carotenoids in the diet.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Chofitol Plus; Daily Nutrilite; Fegalgina; Hepatalgina; Hepatalgina; Metiogen; Palatrobil; *Chile*: Natur-Zin; Natursel-C; *India*: Lunarex; Oxitard; *Ital.*: Evamilk; *Rus.*: Urocholesan (Урохолесан); Urolesan (Уролесан); *UK*: Sciargo; Watershed; *Ukr.*: Urochol (Урохол)†; Urolesan (Уролесан).

Wild Cherry Bark

Corteza de cerezo silvestre; Prunus Serotina; Virginian Prune; Virginian Prune Bark; Wild Black Cherry Bark; Wild Cherry; Черёмуха Поздняя (*Prunus serotina*).
UNII — P3XAO4115F (Prunus serotina); *5D48E975HA* (Prunus serotina *bark*); *A77056YJ4K* (Prunus serotina *fruit*); *XNO4R623ZD* (Prunus serotina *juice*).

Profile

Wild cherry bark is the dried bark of the wild or black cherry, *Prunus serotina* (Rosaceae), known in commerce as Thin Natural Wild Cherry Bark, containing not less than 10% of water-soluble extractive. It has a slight odour and an astringent, aromatic, bitter taste, recalling that of bitter almonds. It contains (+)-mandelonitrile glucoside (prunasin) and an enzyme system, which interact in the presence of water yielding benzaldehyde, hydrocyanic acid, and glucose.

Wild cherry bark, in the form of the syrup, has been used in the treatment of cough but it has little therapeutic value. It has also been used as a flavour.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Bronchial Cough; Echinamide Cold and Cough†; Herbal Cough Syrup†; Honey Blend Herbal Cough Syrup; Mielocol†; *Venez.*: Cerylana.

Wild Indigo

American Indigo; Baptisia; False Indigo; Horsefly Weed; Horseflyweed; Indigo; Indigo Broom; Indigo Sauvage; Indigo Weed; Rattlebush; Rattleweed; Wilder Indigo; Yellow Broom; Yellow Indigo; Yellow Wild Indigo.
ATC Herb — HJ01WB5004 (Baptisia tinctoria: *root*); *HL03AW5002* (Baptisia tinctoria: *root*); *HJ01WA5002* (Baptisia tinctoria: *root*).
UNII — 5K1UO2888Y (Baptisia tinctoria); *7BC6Z38NXU* (Baptisia tinctoria *leaf*); *5EF0HWI5WU* (Baptisia tinctoria *root*).

NOTE. The name Baptisia may also apply to other species of *Baptisia*. The name Indigo is usually applied to the dye traditionally obtained from various species of *Indigofera* (Fabaceae).

Profile

The root of wild indigo, *Baptisia tinctoria* (*Sophora tinctoria*) (Fabaceae), is used for its possible antimicrobial and immunostimulant activity in herbal medicines for respiratory-tract infections and cold symptoms, commonly with Echinacea (p. 2498.1) and Thuja (p. 2629.3). It is also used in topical preparations for skin disorders. Wild indigo has been used in traditional North American native medicine. In large doses it can cause vomiting and diarrhoea.

Wild indigo yields a blue dye that has been used as a substitute for indigo.

Homoeopathy
Wild indigo is also used in homoeopathic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Esberitox N; *Austria*: Esberitox; *China*: Esberitox (施保利通); *Ger.*: Esberitox; *Malaysia*: Esberitox N; *Pol.*: Esberitox N; *Swed.*: Esberitox; *Switz.*: Esberitop; *UK*: Echinacea; Fuerte; Napiers Elixir of Echinacea Complex; Potters Elixir of Echinacea Plus; *Ukr.*: Esberitox (Эсберитокс).

Homoeopathic Preparations. *Austria*: Tonsillopas; toxi-loges; *Canad.*: Arnica-Heel Comp†; Calnor†; Candida Yeast Relief; Cold Sores & Fever Blisters; Echinacea Compositum; Homeo-Form C†; Hylavir FB†; *Fr.*: Boripharm No 22†; *Ger.*: Anovin; Echinacin akut; Hevertotox; Lowe-Komplex Nr 5 Echinacea; Pascoleucyn N; Pascoleucyn; Schworotox; Sinusitis Hevert SL; Tonsillopas; toxi-loges; toxi-loges; toxi-loges; *Neth.*: Febrilite; Grippe-Gastreu R6; Habifac; Nectadyn H; *Switz.*: Influaforce†; Regenaplex Nr 28b; Regenaplex Nr 41a; *Ukr.*: Dr Theiss Gripp Drops (Капли От Гриппа Др. Тайсс)†.

Wild Lettuce

Herba Lactucae Virosae; Laitue Vireuse; Lechuga Montés; Lechuga silvestre; Lechuga Virosa; Poison Lettuce; Латук Дикий.
ATC Herb — HR05DB5006 (Lactuca virosa: *leaf*); *HR05DB5005* (Lactuca virosa: *herb*); *HN05CM5008* (Lactuca virosa: *dry latex*); *HN05CM5010* (Lactuca virosa: *leaf*); *HN05CM5009* (Lactuca virosa: *herb*).

Profile

The wild lettuce, *Lactuca virosa* (Compositae), has been given in herbal medicine as a sedative and antitussive. The dried latex extract (lactucarium; lettuce opium) is also used.

Abuse. A 23-year-old man had sensory distortion, euphoria, and analgesia after ingesting a concentrated aqueous extract of wild lettuce leaves.[1] The authors of the report noted that there had been a report in the literature of a 22-year-old Moroccan woman who died after ingesting wild lettuce stems with 'tilfaf' (*Sonchus* spp). Toxicity has also been associated with intravenous injection of aqueous extracts of wild lettuce.[2]

1. Spadari M, *et al.* Abus de laitue vireuse. *Presse Méd* 2003; 32: 702–3.
2. Mullins ME, Horowitz BZ. The case of the salad shooters: intravenous injection of wild lettuce extract. *Vet Hum Toxicol* 1998; 40: 290–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Herbal Insomnia†; Sirop Cocillana Codeine; *Indon.*: Diasulin; *S.Afr.*: Choats Extract of Lettuce Cough Mixture†; *UK*: Anased; Antibron; Gerard House Somnus; Goodnight; HRI Night; Kalms Sleep; Quiet Life; Quiet Nite; Slumber; Unwind Herbal Nytol; Valerian Passiflora and Hops; *Venez.*: Cerylana; Diamel.

Wild Pansy

European Field Pansy (*Viola arvensis*); European Wild Pansy (*Viola arvensis* or *V. tricolor*); Field Pansy (*Viola arvensis* or *V. tricolor*); Heart's Ease; Heartsease (*Viola tricolor*); Johnny-jump-up (*Viola tricolor*); Keto-orvokki; Love-in-idleness (*Viola tricolor*); Pansy (*Viola tricolor*); Pensée sauvage; Viol; Violae Herba; Violae Tricoloris Herba (viola tricolor); Фиалка Трёхцветная (*Viola tricolor*); Ziele fiołka trójbarwnego (viola tricolor).
ATC Herb — HD11AX5009 (Viola tricolor: *herb*).
UNII — 9Q24RAI43V (Viola tricolor).

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

Ph. Eur. 8: (Wild Pansy (Flowering Aerial Parts); Viola Herba cum Flore). The dried flowering aerial parts of *Viola arvensis* and/or *V. tricolor*. It contains a minimum of 1.5% of flavonoids, expressed as violanthin ($C_{27}H_{30}O_{14}$ = 578.5), calculated with reference to the dried drug. Protect from light.

Profile

Wild pansy, *Viola tricolor* or *V. arvensis* (Violaceae) is used in herbal medicine in topical preparations for minor skin disorders, in particular for seborrhoeic skin diseases. Wild pansy is also included in oral preparations for gastrointestinal and respiratory-tract disorders.

Homoeopathy
Wild Pansy has been used in homoeopathic medicines under the following names: Viola tricolor; Violo tric.

Adverse effects. Haemolysis was reported in a 9-month-old infant with G6PD deficiency given an extract of wild pansy orally.[1]

1. Behmanesh Y, Abdollahi M. Haemolysis after consumption of Viola tricolor. *WHO Drug Inf* 2002; 16: 15–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Bioage Peripheral†; ***Cz.***: Antirevmaticky Caj†; ***Fr.***: Boribel Tisane No 6†; Colitisane†; Depuratif Parnel†; Evacrine; ***Hung.***: Zeatax; ***Ital.***: Neoderma 47; ***Switz.***: Antidry; Viola; ***UK***: Gerard House Skin; Pure Plan.

Homoeopathic Preparations. ***Canad.***: Acne; Eczema L87; ***Cz.***: Lamioflur†; ***Fr.***: Cistus Canadensis Complexe No 86†; Homeodose 24†; Saponaria Compose; Scabiosa Complexe No 87; Staphysagria Complexe No 92†; ***Ger.***: Derma-Plantin†; Ekzevowen; Regenaplex Haut G; ***Neth.***: Chavita 5.

Wild Thyme

Backtimjan; Creeping Thyme; Kangasajuruoho; Mateřídoušková nať (Nať mateřídoušky); Mother of Thyme; Paprastųjų čiobrelių žolė; Quendel; Quendelkraut; Serpolet; Serpylli herba; Тимьян Ползучий.

ATC Herb — HD08AW5004 (Thymus serpyllum: *herb*); *HN05CM5026* (Thymus serpyllum: *herb*); *HA03AW5058* (Thymus serpyllum: *herb*); *HR05WA5057* (Thymus serpyllum: *herb*); *HR05WA5056* (Thymus serpyllum: *essential oil*); *HA03AW5057* (Thymus serpyllum: *essential oil*).

UNII — 86H4S6K51N (Thymus serpyllum); *KXK6I80R8W* (*wild thyme*).

NOTE. Distinguish from Thyme, p. 2630.2.

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

Ph. Eur. 8: (Wild Thyme; Serpylli Herba). The whole or cut, dried, flowering aerial parts of *Thymus serpyllum* containing a minimum of 0.3% v/w of essential oil, calculated with reference to the dried drug. Protect from light.

Profile

Wild thyme (*Thymus serpyllum*, Lamiaceae) is included in herbal medicines for disorders of the upper respiratory tract. Its actions are similar to, but weaker than, those of thyme (p. 2630.2). Commercially, *T. pulegioides* and *T. praecox* subsp. *arcticus* are also offered as *T. serpyllum*.

Wild thyme oil is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Gartech†; ***Austria***: Hustensaft Weleda; Scottopect; ***Belg.***: Thymoseptine; ***Canad.***: Swiss Herb Cough Drops; ***Cz.***: Detsky Caj s Hermankem; Pruduskova; Thymomel; ***Fr.***: Aromasol; Bronchorectine au Citral; Dinacode avec codeine; Nazinette du Docteur Gilbert; ***Ger.***: Weleda Hustenelixier; ***Indon.***: Silex; ***Ital.***: Stenobronchial; Tussamag Complex; Tussamag; ***Rus.***: Pertussin (Пертуссин); Sedativae Species No 3 (Седативный Сбор 3); Stoptussin-Fito (Стоптуссин-фито); ***Switz.***: Tisane contre les refroidissements; ***Ukr.***: Stoptussin Fito (Стоптуссин).

Wild Yam

Atlantic Yam; Colic Root; Rheumatism Root; Дикий Ямс.

ATC Herb — HR05YA5005 (Dioscorea villosa: *root with rhizome*); *HG02WB5002* (Dioscorea villosa: *root with rhizome*); *HM01AW5008* (Dioscorea villosa: *root with rhizome*).

UNII — IWY3IWX2G8 (Dioscorea villosa *root*).

Profile

The root of the wild yam, *Dioscorea villosa* (Dioscoreaceae), is included in herbal remedies for menopausal disorders and rheumatoid arthritis. Wild yam root contains diosgenin, which has been used as a precursor for the chemical synthesis of human steroidal hormones. Some preparations containing wild yam have been promoted as "natural DHEA" but there is little evidence that diosgenin acts as a precursor to hormone synthesis in the human body. Other species of *Dioscorea* are used as food sources and for medicinal purposes.

Homoeopathy

Wild yam has been used in homoeopathic medicines under the following names: Dioscorea villosa; Igname Sauvage; Zottige Yamswurzel.

References.

1. Komesaroff PA *et al.* Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric* 2001; 4: 144–50.
2. Final report of the amended safety assessment of Dioscorea Villosa (Wild Yam) root extract. *Int J Toxicol* 2004; 23: 49–54.
3. Wojcikowski K, *et al.* Dioscorea villosa (wild yam) induces chronic kidney injury via pro-fibrotic pathways. *Food Chem Toxicol* 2008; 46: 3122–31.
4. Wojcikowski K, *et al.* An in vitro investigation of herbs traditionally used for kidney and urinary system disorders: potential therapeutic and toxic effects. *Nephrology (Carlton)* 2009; 14: 70–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Advanced Menopause Care; Cimicifuga Compound; Cramplex; Dyzco†; Femi-Nan; Feminine Herbal Complex; Soy Power Plus†; Wild Yam Complex; ***Canad.***: Herbal Laxative†; Libeeda for Women; Milk Thistle Extract Formula; Natural HRT; Painease; ***Fr.***: Androlistica; Biopause; Menolistica; ***Ital.***: Ri-Donna; ***Singapore***: Androlistica; ***Ukr.***: Lifemin (Лайфемин).

Homoeopathic Preparations. ***Canad.***: Colic; Hylands Kinder-CL†; Kid's Colic; Motherwort Combination 1†; ***Fr.***: Aloe Compose; Conium Complexe No 36†; ***Ger.***: Dolo-Injektopas; Homviohepan; Phytocortal; ***Switz.***: Regenaplex Nr. 80aN; ***USA***: Estrex.

Xanthine-containing Beverages

Xantina, bebidas con; Ксантинсодержащие Напитки.

Uses and Administration

Xanthine-containing beverages including chocolate, coffee, cocoa, cola, maté, and tea are widely consumed and have a mild stimulant effect on the CNS. The primary xanthine constituent is caffeine (p. 1203.3) but other xanthine derivatives such as theobromine (p. 1229.2) and theophylline (p. 1229.3) may also be present; cocoa and chocolate contain significant amounts of theobromine.

Coffee is the kernel of the dried ripe seeds of *Coffea arabica*, *C. liberica*, *C. canephora* (robusta coffee), and other species of *Coffea* (Rubiaceae), roasted until it acquires a deep brown colour and a pleasant characteristic aroma. It contains about 1 to 2% of caffeine. Coffee has been used in the form of an infusion or decoction as a stimulant and as a flavour in some pharmaceutical preparations. A decoction is used as a beverage containing up to about 100 mg of caffeine per 100 mL. Preparations of instant coffee may contain up to 40% less caffeine while decaffeinated preparations may contain only up to about 3 mg per 100 mL.

Kola (cola, cola seeds, kola nuts) is the dried cotyledons of *Cola nitida* and *C. acuminata* (Sterculiaceae), containing up to about 2.5% of caffeine and traces of theobromine. Kola is used in the preparation of cola drinks which may contain up to 20 mg of caffeine per 100 mL.

Maté (Paraguay Tea) is the dried leaves of *Ilex paraguensis* (Aquifoliaceae), containing 0.2 to 2% of caffeine and traces of theobromine. Maté is less astringent than tea and is extensively used as a beverage in South America.

Tea (thea, chá, thé, tee) is the prepared young leaves and leaf-buds of *Camellia sinensis* (=*C. thea*) (Theaceae). It contains 1 to 5% of caffeine, up to 24% of tannin, and small amounts of theobromine and theophylline. Tea is used in an infusion as a beverage containing up to about 60 mg of caffeine per 100 mL.

Guarana consists of the crushed seeds of *Paullinia cupana* var *sorbilis* (Sapindaceae). Caffeine appears to be its major active ingredient which was once termed guaranine. Herbal preparations include a beverage or liquid extract and may contain 5% caffeine.

Homoeopathy

Coffee has been used in homoeopathic medicines under the following names: Coffea arabica; Coffea; Coffea cruda; Coff. cr.; Coffea tosta.

Kola has been used in homoeopathic medicines under the following names: Cola; Sterculia acuminata; Sterculia acum.

Maté has been used in homoeopathic medicines under the following names: Ilex paraguayensis; Ile. para.; Ilex paraguariensis; Ilex parag.

Guarana has been used in homoeopathic medicines.

Diabetes mellitus. Regular coffee consumption has been reported[1-6] to reduce the risk of developing type 2 diabetes mellitus, although it is not clear whether this effect is due to caffeine or some other constituent in coffee.

1. Salazar-Martinez E, *et al.* Coffee consumption and risk for type 2 diabetes mellitus. *Ann Intern Med* 2004; 140: 1–8.
2. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA* 2005; 294: 97–104.
3. van Dam RM, *et al.* Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. *Diabetes Care* 2006; 29: 398–403.
4. Iso H, *et al.* The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. *Ann Intern Med* 2006; 144: 554–62.
5. Pereira MA, *et al.* Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28 812 postmenopausal women. *Arch Intern Med* 2006; 166: 1311–16.
6. Smith B, *et al.* Does coffee consumption reduce the risk of type 2 diabetes in individuals with impaired glucose? *Diabetes Care* 2006; 29: 2385–90.

Adverse Effects

The adverse effects of xanthine-containing beverages are largely due to their caffeine (p. 1203.3), theophylline (p. 1229.3), and theobromine (p. 1229.2) content. Common adverse effects are sleeplessness, anxiety, tremor, palpitations, and withdrawal headache.

Breast feeding. For references to the effects of caffeinated beverages in breast feeding, see under Caffeine, p. 1205.2.

Effects on the heart. A meta-analysis of published studies found no evidence of an association between coffee consumption and the development of coronary heart disease,[1] and a large cohort study in men followed up for 14 years and women for up to 20 years also found no evidence of a link.[2] Expert opinion in the UK[3] has been that the evidence that caffeine or coffee consumption contributes to coronary heart disease development is inconsistent. Coffee prepared by boiling, as is the practice in Scandinavia for example, does raise serum cholesterol concentrations due to the presence of the diterpenes cafestol and kahweol, and coffee made in a cafetière (French press) has a similar effect, but filtered coffee does not, as the hypercholesterolaemic fraction does not pass a paper filter.[4] A case-control study has suggested a relationship between consumption of boiled, but not filtered, coffee and incidence of a first non-fatal myocardial infarction.[5] Others have raised concern that the potential pressor effect of caffeine itself may be a cardiovascular risk factor,[6] but as mentioned above there is little evidence for this. A large prospective cohort study[7] found no association between dietary caffeine and risk of atrial fibrillation or flutter.

Tea drinking has not been associated with increased cardiovascular risk[3]—indeed, its polyphenol content has been suggested to have beneficial antoxidant effects.[8,9]

1. Myers MG, Basinski A. Coffee and coronary heart disease. *Arch Intern Med* 1992; 152: 1767–72.
2. Lopez-Garcia E, *et al.* Coffee consumption and coronary heart disease in men and women: a prospective cohort study. *Circulation* 2006; 113: 2045–53.
3. DoH. Nutritional aspects of cardiovascular disease. Report of the cardiovascular review group committee on medical aspects of food policy. Report on health and social subjects no. 46. London: HMSO, 1994.
4. Urgert R, *et al.* Comparison of effect of cafetière and filtered coffee on serum concentrations of liver aminotransferases and lipids: six month randomised controlled trial. *BMJ* 1996; 313: 1362–6.
5. Hammar N, *et al.* Association of boiled and filtered coffee with incidence of first nonfatal myocardial infarction: the SHEEP and the VHEEP study. *J Intern Med* 2003; 253: 653–9.
6. James JE. Is habitual caffeine use a preventable cardiovascular risk factor? *Lancet* 1997; 349: 279–81.
7. Frost L, Vestergaard P. Caffeine and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005; 81: 578–82.
8. Luo M, *et al.* Inhibition of LDL oxidation by green tea extract. *Lancet* 1997; 349: 360–1.
9. Geleijnse JM, *et al.* Tea flavonoids may protect against atherosclerosis: the Rotterdam study. *Arch Intern Med* 1999; 159: 2170–4.

Effects on the muscles. Severe myositis in an elderly man who drank around 14 litres of tea daily was attributed to hypokalaemia produced by the xanthine content of the beverage.[1] The patient improved after intravenous potassium replacement and subsequently remained well with a reduction in tea intake.

1. Trewby PN, *et al.* Teapot myositis. *Lancet* 1998; 351: 1248.

Malignant neoplasms. A review of available data did not suggest a clinically significant association between the regular use of coffee and the development of cancer of the lower urinary tract in men or women.[1]

1. Viscoli CM, *et al.* Bladder cancer and coffee drinking: a summary of case-control research. *Lancet* 1993; 341: 1432–7.

Interactions

The possibility of synergistic effects in patients receiving xanthines who consume large amounts of xanthine-containing beverages should be borne in mind.

Antipsychotics. Xanthine-containing beverages have been reported to precipitate some antipsychotic drugs from solution *in vitro*, but do not appear to alter antipsychotic concentrations *in vivo*. For references, see p. 1053.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ollantay; Radite; ***Austria***: Veregen; ***Braz.***: Guarafort†; ***Chile***: Revaleskin; ***Fr.***: Camiline; ***Ger.***: Carbo Konigsfeld; Veregen; ***Ital.***: Categ; ***Neth.***: Veregen; ***Spain***: Veregen; ***Switz.***: Veregen; ***UK***: Yariba; ***USA***: Tegreen.

Multi-ingredient Preparations. ***Arg.***: Adelgazar; ADX; Centella Incaico; Cesagrip; Delgacin; Desgras Complex; Energizante Vital con ginseng; Energizante; Energy Plus; Ginkgo Biloba Memo Diates†; Guarana Diates†; Guaranup; Ikx Gel Reductor†; Radite Plus; Supervitaminico†; Vitalfort Antioxidante; Vitalsex; Yerba Diet; Zinc Antioxidante + Guarana; ***Austral.***: 3B Beer Belly Buster†; Avena Complex†; Femme-F; Flavonoid Complex; GR² Control Thermogenic Enhancer; Hairy Lemon; Irontona†; Liver

Detox; Metabolift Fat Burner; PM Joint-Care; VIG; Vitanox; Vitatona†; *Braz.*: Gero Forte†; *Canad.*: Super Energex Plus†; Trim-Fit†; *Chile*: Cellenergy; Draineur; *Fr.*: Alibi; Alpharegul Femme; Amana Cellium; Anti-oxydant F4; Biotone; Drainuryl; Dynabiane; Elusanes Starphyt†; Expuryl; Fliigel†; Gerimax adultes†; Guaramate†; Hydrastart; Imedeen Prime Renewal†; Mediflor no 1; Mincifit†; Photoderm; Quintonine†; Santane O1; Sun Vue; Tavmet; Tealine†; Teaslim†; Tonactil†; Uromil; Vitrecor; YSE†; *Ger.*: Myrrhinil-Intest; Repursan†; *Hong Kong*: Mega-Antioxidant†; Sessoforte†; Wari-Procomil†; Wellman†; *Hung.*: Antifront; Antifront; Menofit; Sam-Ginseng Royal; Vensaxa; *India*: Absolut; Dayvital; Gardian; Gen-One; Lycogreen; Lyconet Green; Morvit; Multivite Gold; Multivite Woman; Nislutin; Nutiva-Lyco; Obedeuce; *Indon.*: Antox; F-Slim†; Lycoq†; Naturlesterol; Oncoxin; Oxan; Radiblock; *Irl.*: Avena Sativa Comp; Biofreeze†; *Israel*: Biolax Protect; Coltect†; *Ital.*: Almavigor; Altadrine Firming†; Biomineral 5-Alfa Shampoo; Biomineral 5-Alfa; Calmason; Dam; Idren; Linfolipase; Snell Cell†; Valcap; Vitalmix Complex; Vitalmix Fast; *Jpn*: Senkyuchachosan; *Malaysia*: Glow; *Mex.*: Noxivid†; Zumba; *Philipp.*: Fit-N-Trim; Fitrum; Gloww; Jamieson Total Energy; Lungcaire Plus; Memory DD†; Nutrafit; *Pol.*: Cardiol C; Penigra; Tobacoff; *Rus.*: Insti (Инсти); *S.Afr.*: Avena Sativa Comp†; *Singapore*: Berocca Boost; Bio-Taches†; Glow; Hepasil DTX†; Mincifit Body Shaper; *Spain*: Enofosforina Vigor†; Exodren; Fitosvelt†; Rimagrip†; Tealine; *Switz.*: Enuton†; Tonique D liquide†; *Turk.*: Keten; *UK*: Avena Sativa Comp; Biofreeze; Chlorophyll; Cleansing Herbs; Daily Fatigue Relief; Damiana and Kola Tablets; Glykola; Lion Cleansing Herbs; Pure Plan; S.P.H.P.; Strength; Zotrim; *Ukr.*: Antifront (Антифронт); Antifront (Антифронт); Grinvitals Cereloba Plus (Гринвитал Церелоба Плюс); Insti (Інсті); Lipomin (Липомин); Liponorm (Липонорм); Sadifit (Садифит); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Cardio Tone; Cardiopress; Diabetiks; Immunicare; Macu-Trition; PowerMate; *Venez.*: Demerung; Ocoxin.

Homoeopathic Preparations. *Austral.*: Childrens Sleep; Elimitona; Sleep & Insomnia Relief; *Austria*: Ambra Med Complex; Iris Med Complex; Notta; Nux Med Complex; *Canad.*: Calsom†; Comp-Drops 7 Sleepless†; Den 141†; Homeo-Form CA†; Homeoknop Bioactiv O Weight Loss Aid†; Hylands Kinder-T†; Nervita: Passiflora Complex†; Sedilor†; Tee Complex†; Teething; *Chile*: Bioactiv Z; *Fr.*: Budyne†; Noctium; Passiflora Compose; Poconeol no 75; Sativol†; Selenium Complexe No 99; Somnidoron; Tonique Vegetal; *Ger.*: Aktivon; Avena sativa comp†; Biodolor; Cranio-cyl Ho-Len-Complex; Dormi-cyl L Ho-Len-Complex; Dormi-Gastreu S R14; dysto-loges N; dysto-loges S; Hevert-Activon Kreislauftropen†; Infinerval; Liquidorm N; Lycoaktin; Nervo-Plantin†; Neurexan; Pflugerplex Gelsemium; Psychoneuroticum (Rowo-578)†; Seda-Do; Sedakatt; *Neth.*: Kruidvat Homeopathie Nachtrust†; Nervival; Sativol†; Weleda Avena Valeriana; *Rus.*: Notta (Нотта); *Switz.*: Nelsons Nocturna†; Sleepium; *UK*: Noctura; *Ukr.*: Notta (Нотта); *USA*: Preferred Remedies Sleep.

Xanthopterin

Ксантоптерин.
2-Amino-4,6-dihydroxypteridine.
$C_6H_5N_5O_2$=179.1
CAS — 119-44-8.
UNII — V66551EU1R.

Profile

Xanthopterin is a natural pigment that has been used topically in the management of eye disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Xantervit Antibiotico; Xantervit Eparina; Xantervit.

Xylazine *(BAN, rINN)*

Ksylatsiini; Xilazina; Xylazin; Xylazinum; Ксилазин.
N-(5,6-Dihydro-4*H*-1,3-thiazin-2-yl)-2,6-xylidine.
$C_{12}H_{16}N_2S$=220.3
CAS — 7361-61-7.
ATC Vet — QN05CM92.
UNII — 2KFG9TP5V8.

Pharmacopoeias. In *US*.

USP 36: (Xylazine). Colourless to white crystals. Sparingly soluble in acetone, in chloroform, and in dilute acid; insoluble in dilute alkali. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Xylazine Hydrochloride *(BANM, USAN, rINNM)*

Bay-Va-1470; Hidrocloruro de xilazina; Ksylatsiinihydrokloridi; Xilazina, hidrocloruro de; Xilazin-hidroklorid; Xylazine, chlorhydrate de; Xylazin-hydrochlorid; Xylazinhydroklorid; Xylazini Hydrochloridum; Ксилазина Гидрохлорид.
$C_{12}H_{16}N_2S, HCl$=256.8
CAS — 23076-35-9.
UNII — NGC3S0882S.

Pharmacopoeias. In *US*.

Eur. (see p. vii) includes for veterinary use only.

Ph. Eur. 8: (Xylazine Hydrochloride for Veterinary Use; Xylazine Hydrochloride BP(Vet) 2014). A white or almost white, crystalline, hygroscopic powder. Freely soluble in water and in dichloromethane; very soluble in methyl alcohol. A 10% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Xylazine Hydrochloride). Colourless to white crystals. Sparingly soluble in acetone, in methyl alcohol, and in dilute acid; insoluble in dilute alkali. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Xylazine is a sedative, analgesic, and muscle relaxant used in veterinary medicine. The hydrochloride is used similarly. Abuse has been reported.

Adverse effects. Reports[1-7] of toxicity and abuse associated with xylazine. Bradycardia, hypotension, and coma were associated with the self-administration of 200 mg of xylazine. Treatment was supportive.[1] Systemic toxicity has been reported after accidental ocular exposure.[6]

1. Samanta A, *et al.* Accidental self administration of xylazine in a veterinary nurse. *Postgrad Med J* 1990; **66**: 244–5.
2. Mittleman RE, *et al.* Xylazine toxicity—literature review and report of two cases. *J Forensic Sci* 1998; **43**: 400–2.
3. Hoffmann U, *et al.* Severe intoxication with the veterinary tranquilizer xylazine in humans. *J Anal Toxicol* 2001; **25**: 245–9.
4. Capraro AJ, *et al.* Severe intoxication from xylazine inhalation. *Pediatr Emerg Care* 2001; **17**: 447–8.
5. Elejalde JI, *et al.* Drug abuse with inhalated xylazine. *Eur J Emerg Med* 2003; **10**: 252–3.
6. Velez LI, *et al.* Systemic toxicity after an ocular exposure to xylazine hydrochloride. *J Emerg Med* 2006; **30**: 407–10.
7. Liu CM, *et al.* Xylazine abuse: a rare cause of syncope. *Clin Toxicol* 2007; **45**: 309–11.

Xylose

Azúcar de la madera; Ksiloze; Ksyloosi; Ksyloza; Wood Sugar; Ксилоза; Древесный Сахар; D-xilosa; Xilosa; Xilóz; Xylos; Xylosa; D-Xylose; Xylosum.
α-D-Xylopyranose.
$C_5H_{10}O_5$=150.1
CAS — 58-86-6; 6763-34-4.
UNII — A1TA934AKO.

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

Ph. Eur. 8: (Xylose). A white or almost white crystalline powder or colourless needles. Freely soluble in water; soluble in hot alcohol.

USP 36: (Xylose). Odourless, colourless needles or white crystalline powder. Very soluble in water; slightly soluble in alcohol. Store in airtight containers at a temperature of 15 degrees to 30 degrees.

Profile

Xylose has been used for the investigation of absorption from the gastrointestinal tract. In the absence of malabsorption, about 35% of a 5-g oral dose and about 25% of a 25-g oral dose are reported to be excreted in the urine within 5 hours. It has been given orally, usually in a dose of either 5 or 25 g, with up to 700 mL of water. The amount recovered in the urine is estimated and used to assess any malabsorption. Adjustment may have to be made for renal impairment. Xylose may cause some gastrointestinal discomfort with large doses. Other drugs may affect the absorption of xylose and interfere with the xylose test.

The test has been adapted to measure blood-xylose concentrations.

References.

1. Craig RM, Ehrenpreis ED. D-xylose testing. *J Clin Gastroenterol* 1999; **29**: 143–50.

Precautions. Preparations that contain, or are metabolised to, xylose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2]

1. Medicines and Healthcare products Regulatory Agency. Medical device alert: ref MDA/2007/058 issued 19 July 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 16/08/10)

Yellow Dock

Curly Dock; Evilloriva; Lengua de vaca; Sour Dock; Щавель Курчавый (*Rumex crispus*).
UNII — S9T422Q956 (Rumex crispus); 9N1RM2S62C (Rumex crispus root).

NOTE. The name sour dock has also been used for sorrel (p. 2620.3).

Profile

Yellow dock, the root of *Rumex crispus* (Polygonaceae) has laxative and choleretic properties. It is used for constipation, jaundice, and chronic skin disorders.

Homoeopathy

Yellow Dock has been used in homoeopathic medicines under the following names: Rumex; Rumex crispus; Rumex crisp; Rumex c.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Arctium & Zinc Compound; Colax†; Colax; DermaCo; Haemo-Red; *Canad.*: Herbanat†; Kalenite†; *Port.*: Stodal; *Swed.*: Sinova; *UK*: Skin Eruptions Mixture.

Homoeopathic Preparations. *Austral.*: Respatona Dry Cough & Nasal Congestion; *Canad.*: Arum Triphyllum Plex†; Brocosin; Bronchial Cough; Hylaquell BC; Yellow Dock Combination†; *Chile*: Pertussin; *Cz.*: Stodal; *Fr.*: Arum Triphyllum Compose; Spirodrine; Stodal; Stodal; *Hung.*: Stodal; *Neth.*: Nectadyn H; Stodal; *Rus.*: Stodal (Стодаль); *Switz.*: Stodal; *UK*: Pyrethrum Spray; *Ukr.*: Stodal (Стодаль).

Ylang Ylang Oil

Cananga Oil; Ylang-ylang Oil.

Profile

Ylang ylang oil from the flowers of ylang ylang (*Cananga odorata*, Annonoceae), is used in perfumery, as a flavouring agent, and in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Paranix; *Fr.*: Arthro; *Ger.*: Paranix; *Singapore*: Teenstick; *Switz.*: Paranix; *UK*: Teenstick.

Yogurt

Jaurt; Iogurt; Joghurt; Jogurt; Jogurtas; Jogurtti; Yaourt; Yoghourt; Yoghurt; Yogur; Yoğurt; Кисело Мляко; Йогурт.

Profile

Yogurt is produced by bacterial fermentation of milk and is a source of protein, calcium, and vitamins. It has been used in preparations for gastrointestinal disorders and in nutritional supplements. It may also be used as a source of lactic-acid producing organisms (see p. 2596.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Herbal Laxative plus Yogurt†; *Fr.*: Benetransit†; *Ital.*: Lactivis.

Yucca

Yuca; Юкка.

Profile

Various species of *Yucca* (Liliaceae), including Mohave yucca (*Y. schidigera*; *Y. mohavensis*), the Joshua tree (*Y. brevifolia*; *Y. arborescens*), and bear grass (*Y. filamentosa*) have been used in herbal medicine and as foods.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Bronquiogen†.

Homoeopathic Preparations. *Fr.*: Yucca Complexe No 110; *Ger.*: Heparanox H; Leber Albin.

Zanthoxylum Fruit

Prickly Ash Berries; Sichuan Pepper; Szechuan Pepper; Зантоксилум Перечный (*Zanthoxylum piperitum*); Zanthoxylum, fruto de.
UNII — Y8IKP41338 (Zanthoxylum piperitum); 7PFC2VA251 (Zanthoxylum piperitum fruit pulp); 728JDI7G4M (Zanthoxylum piperitum fruit rind).

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Zanthoxylum fruit is the pericarp of the ripe fruit of *Zanthoxylum piperitum* (*Xanthoxylum piperitum*) (Rutaceae) or other species of *Zanthoxylum*. It contains about 3.3% v/w of essential oil.

Zanthoxylum (BPC 1934) (Toothache Bark; Xanthoxylum) is the dried bark of the northern prickly ash, *Z. americanum*, or the southern prickly ash, *Z. clavaherculis*. Both varieties contain a complex mixture of components, including benzophenanthridine alkaloids; northern prickly ash also contains coumarins.

Zanthoxylum fruit has carminative properties and has been used for rheumatic disorders and as a culinary spice. Zanthoxylum bark has been used similarly, but there is some concern about the potential toxicity of the benzophenanthridine alkaloids which it contains, and some authorities consider that it should not be recommended.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: For Peripheral Circulation Herbal Plus Formula 5†; *Fr.*: Node K; Phytheol Forcet†; *Jpn*: Daikenchuto; Tokito; *UK*: Daily Overwork & Mental Fatigue Relief; Peerless Composition Essence; Tabritis.

Zilpaterol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de zilpaterol; RU-42173 (base or hydrochloride); Zilpatérol, Chlorhydrate de; Zilpateroli Hydrochloridum; Зилпатерола Гидрохлорид.

(±)-*trans*-4,5,6,7-Tetrahydro-7-hydroxy-6-(Isopropylamino) imidazo[4,5,1-*jk*][1]benzazepin-2(1*H*)-one hydrochloride.
$C_{14}H_{19}N_3O_2,HCl$=297.8
CAS — 117827-79-9 (zilpaterol); 119520-05-7 (zilpaterol); 119520-06-8 (zilpaterol hydrochloride).
UNII — EX8IEP25JU.

Profile

Zilpaterol hydrochloride is a beta$_2$-agonist. It is employed in the USA and some other countries as an animal-feed additive to promote weight gain but such use is not permitted in the EU. It has anabolic properties and may be subject to abuse in sport.

Zinc Nitrate

Azotan Cynku; Nitrate de zinc; Zinc Dinitrate; Zinknitraat; Zinknitrat; Цинков Динитрат.
$Zn(NO_3)_2$=189.4
CAS — 7779-88-6 (zinc nitrate); 10196-18-6 (zinc nitrate hexahydrate).
UNII — EDO66F5U49.

Profile

Zinc nitrate has oxidising and corrosive properties. It has various industrial uses, including electro-galvanizing and as a mordant in dyeing. It has also been used as the hexahydrate in preparations for the treatment of benign vaginal lesions.

For more information on zinc and its salts, see p. 2126.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Pol.*: Solcogyn; *Rus.*: Solcovagin (Солковагин); *Switz.*: Solcogyn; *Ukr.*: Solcovagin (Солковагин).

Zinc Ricinoleate

Рицинолеат Цинка.
$(C_{18}H_{33}O_3)_2Zn$=660.3
CAS — 13040-19-2.
UNII — BOH1Z111JZ.

Profile

Zinc ricinoleate is used in preparations to combat body odour including underarm, colostomy, and ileostomy deodorant products. It is also used as a deodoriser in laundry products.

Preparations

Proprietary Preparations (details are given in Volume B)

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

Multi-ingredient Preparations. *Austral.*: Banish II.

Zirconium

Circonio; Zirconio; Zirkonium; Цирконий.
Zr=91.224
CAS — 7440-67-7 (zirconium); 1314-23-4 (zirconium dioxide); 60676-90-6 (zirconium lactate); 7699-43-6 (zirconium oxychloride).
UNII — C6V6S92N3C.

Profile

Zirconium and its compounds e.g. zirconium dioxide, zirconium lactate, and zirconium oxychloride, have been used in deodorant preparations; the dioxide is also used in dentistry. There have been reports of hypersensitivity reactions with granulomas. Zirconium dioxide has also been used as a contrast medium.

Adverse effects. A report[1] of pulmonary fibrosis associated with inhalation of a polishing agent containing mainly zirconium dioxide with quartz.

1. Bartter T. *et al.* Zirconium compound-induced pulmonary fibrosis. *Arch Intern Med* 1991; 151: 1197–1201.

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