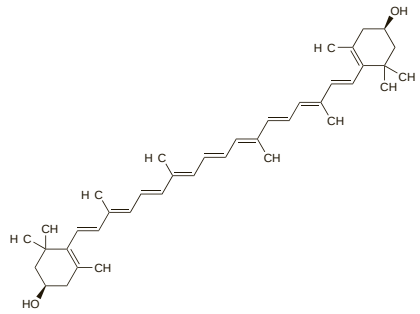
Lievitovit; Preparazione H; Sillix C†; Sillix†; ***Neth.:*** Sperti Preparation H; ***Pol.:*** Preparation H†; Vegevit B ; ***Port.:*** Bioregime Fort†; Sperti Preparacao H; ***Rus.:*** Preparation H (Препарейшн Эйч); ***S.Afr.:*** Preparation H; ***Spain:*** Preparacion H; ***Switz.:*** A Vogel Capsules polyvitamineesf†; Carbolevure; Sperti Preparation H; ***UK:*** Bio-Strath Artichoke Formula; Bio-Strath Valerian Formula; Bio-Strath Willow Formula; Brewers Yeast; Preparation H; Tonic Yeast; Yeast Vite; ***USA:*** Medicone†; Preparation H; Rectagene Medicated Balm; Wyanoids Relief Factor; ***Venez.:*** Wampole†.

Zeaxanthin

Anchovyxanthin; Zeaxanthol. (3*R*,3′*R*)-β,β-Carotene-3,3′-diol.

Зеаксантин

$C_{40}H_{56}O_2$ = 568.9.
CAS — 144-68-3.



Profile

Zeaxanthin is a naturally occurring carotenoid that is promoted as a dietary supplement for age-related macular degeneration (p.785).

◊ References.

1. Mares-Perlman JA, *et al.* The body of evidence to support a protective role for lutein and zeaxanthin in delaying chronic disease: overview. *J Nutr* 2002; **132** (suppl): 518S–524S.
2. Mozaffarieh M, *et al.* The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J* 2003; **2:** 20.
3. Hartmann D, *et al.* Plasma kinetics of zeaxanthin and 3′-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. *Am J Clin Nutr* 2004; **79:** 410–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Indon.:*** Eyevit; Matovit Fifty; Nuvision; ***Mex.:*** Snelvit.

Zinc

Cynk; Zincum; Zink.

Zn = 65.38.
CAS — 7440-66-6.

Zinc Acetate

Cink-acetát-dihidrát; Cinko acetatas dihidratas; Cynku octan; E650; Octan zinečnatý dihydrát; Sinkkiasetaatti; Zinc (acétate de) dihydraté; Zinc, acetato de; Zinci Acetas; Zinci acetas dihydricus; Zinkacetat.

$(CH_3CO_2)_2Zn,2H_2O$ = 219.5.
CAS — 557-34-6 (anhydrous zinc acetate); 5970-45-6 (zinc acetate dihydrate).
ATC — A16AX05.
ATC Vet — QA16AX05.

NOTE. Zinc Acetate, Basic is *rINN*.

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

Ph. Eur. 6.2 (Zinc Acetate Dihydrate; Zinc Acetate BP 2008). A white or almost white, crystalline powder or leaflets. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 5.8 to 7.0. Store in nonmetallic containers.

USP 31 (Zinc Acetate). White crystals or granules having a slight acetous odour. Is slightly efflorescent. Soluble 1 in 2.5 of water and 1 in 30 of alcohol; freely soluble in boiling alcohol. pH of a 5% solution in water is between 6.0 and 8.0. Store in airtight containers.

Zinc Chloride

Chlorid zinečnatý; Cink-klorid; Cinko chloridas; Cynku chlorek; Sinkkikloridi; Zinc, chlorure de; Zinc, cloruro de; Zinci chloridum; Zincum Chloratum; Zinkklorid.

$ZnCl_2$ = 136.3.
CAS — 7646-85-7.
ATC — B05XA12.
ATC Vet — QB05XA12.

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

Ph. Eur. 6.2 (Zinc Chloride). A white or almost white, deliquescent, crystalline powder or cast in white or almost white sticks. Very soluble in water; freely soluble in alcohol and in glycerol. An approximately 10% solution in water has a pH of 4.6 to 5.5. Store in nonmetallic containers.

USP 31 (Zinc Chloride). A white or practically white, odourless, crystalline powder, or white or practically white crystalline granules. May also be in porcelain-like masses or moulded into cylinders. It is very deliquescent. Soluble 1 in 0.5 of water, 1 in 1.5 of alcohol, and 1 in 2 of glycerol. Its solution in water or in alcohol is usually slightly turbid, but the turbidity disappears when a small quantity of hydrochloric acid is added. A 10% solution in water is acid to litmus. Store in airtight containers.

Turbidity. Zinc chloride almost always contains some oxychloride which produces a slightly turbid aqueous solution. Turbid solutions, except when intended for ophthalmic use, may be cleared by adding gradually a small amount of dilute hydrochloric acid. Solutions of zinc chloride should be filtered through asbestos or sintered glass, since they dissolve paper and cotton wool.

Zinc Citrate

Zinc Citrate Trihydrate. 2-Hydroxy-1,2,3-propanetricarboxylic acid zinc salt.

Цитрат Цинка

$C_{12}H_{10}O_{14}Zn_3,3H_2O$ = 628.4.
CAS — 546-46-3.

Pharmacopoeias. In *Chin.*

Zinc Gluconate

Zinc, gluconate de; Zinc, gluconato de; Zinci gluconas.

$C_{12}H_{22}O_{14}Zn$ = 455.7.
CAS — 4468-02-4.
ATC — A12CB02.
ATC Vet — QA12CB02.

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

USP 31 (Zinc Gluconate). White or practically white powder or granules. Soluble in water; very slightly soluble in alcohol. pH of a 1% solution in water is between 5.5 and 7.5.

Zinc Sulfate

Çinko Sülfat; Cinko sulfatas; Cink-szulfát; Cynku siarczan; Sinkkisulfaatti; Síran zinečnatý; Zinc, sulfate de; Zinc, sulfato de; Zinc Sulphate; Zinci sulfas; Zincum Sulfuricum; Zinksulfat.

$ZnSO_4,7H_2O$ = 287.5.
CAS — 7733-02-0 (anhydrous zinc sulfate); 7446-20-0 (zinc sulfate heptahydrate).
ATC — A12CB01.
ATC Vet — QA12CB01.

NOTE. 'White vitriol' or 'white copperas' is crude zinc sulfate. ZSU is a code approved by the BP 2008 for use on single unit doses of eye drops containing zinc sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *Viet.*
Eur. also includes the monohydrate and the hexahydrate.
US includes the monohydrate and the heptahydrate in one monograph.

Ph. Eur. 6.2 (Zinc Sulphate Heptahydrate; Zinci Sulfas Heptahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 6.2 (Zinc Sulphate Hexahydrate; Zinci Sulfas Hexahydricus). Colourless, transparent, crystals or a white or almost white, crystalline powder; efflorescent. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic airtight containers.

Ph. Eur. 6.2 (Zinc Sulphate Monohydrate; Zinci Sulfas Monohydricus). Colourless, transparent, crystals or a white or almost white crystalline powder. Very soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.4 to 5.6. Store in nonmetallic containers.

USP 31 (Zinc Sulfate). It contains one or seven molecules of water of hydration. Colourless, transparent, prisms, or small needles. May occur as a white, granular, crystalline powder. It is odourless and is efflorescent in dry air. Very soluble in water (heptahydrate); freely soluble in water (monohydrate); practically insoluble in alcohol (monohydrate); insoluble in alcohol (heptahydrate); freely soluble in glycerol (heptahydrate). Its solutions are acid to litmus. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of zinc salts (the gluconate and sulfate) given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals.

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Prolonged use of high doses of zinc supplements, orally or parenterally, leads to copper deficiency with associated sideroblastic anaemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in haemodialysis solutions. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate (p.1462).

Metal fume fever is an occupational disease associated with inhalation of freshly-oxidised metal fumes, most commonly from zinc, iron or copper. It is characterised by chills, fever, cough, dyspnoea, myalgia, and chest pain, and is generally self-limiting and does not appear to be associated with long-term sequelae.

Effects on the blood. There have been reports[1-3] of anaemia, leucopenia, and neutropenia in patients consuming excessive amounts of zinc supplements for acne. A patient given zinc-containing enteral feeds as well as zinc supplementation was diagnosed with sideroblastic anaemia due to zinc toxicity.[4] All patients were copper-deficient,[1-4] despite supplementation with copper in one case.[4]

1. Porea TJ, *et al.* Zinc-induced anemia and neutropenia in an adolescent. *J Pediatr* 2000; **136:** 688–90.
2. Igic PG, *et al.* Toxic effects associated with consumption of zinc. *Mayo Clin Proc* 2002; **77:** 713–16.
3. Salzman MB, *et al.* Excessive oral zinc supplementation. *J Pediatr Hematol Oncol* 2002; **24:** 582–4.
4. Irving JA, *et al.* Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation. *Can Med Assoc J* 2003; **169:** 129–31.

Hypersensitivity. Report of a patient who developed palmoplantar pustulosis about 1 year after receiving dental fillings containing zinc.[1] Zinc hypersensitivity was confirmed by *in vitro* and patch testing. Complete remission occurred on replacing the dental fillings.

1. Yanagi T, *et al.* Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005; **366:** 1050.

Parenteral nutrition. Zinc was found to be a common contaminant of various components used for total parenteral nutrition (TPN), and rubber stoppers or glass may have been the source.[1] Levels of zinc found may exceed daily requirements even before the addition of supplementary zinc. The authors suggested it may be important to routinely monitor zinc status in patients receiving long-term TPN, particularly infants and children.

1. Hak EB, *et al.* Chromium and zinc contamination of parenteral nutrient solution components commonly used in infants and children. *Am J Health-Syst Pharm* 1998; **55:** 150–4.

Interactions

The absorption of zinc may be reduced by iron supplements (see also Absorption, under Pharmacokinetics, below) , penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones (see Antacids and Metal Ions, under Interactions of Ciprofloxacin, p.246), iron, penicillamine, and tetracyclines (p.348).

Pharmacokinetics

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

Absorption. Although zinc deficiency (see Deficiency States, under Uses and Administration, below) in some cases may be due to inadequate dietary intake, inhibitors of zinc absorption may also be causative.[1] *Phytates*, which are present in cereals, corn, legumes, and rice, inhibit zinc absorption. The animal *protein* in beef, eggs, and cheese counteracts the inhibitory effect of phytate, whereas the casein in milk decreases zinc absorption. Proteins also often contain other constituents such as inorganic *phosphate* that can negatively affect zinc absorption. Long-term use of *calcium* supplements has no effect on zinc status, but dietary calcium may form insoluble complexes with phytate and zinc, thus decreasing the absorption of zinc. *Iron* can reduce zinc absorption, although the effect is apparent only at a very high

ratio of iron to zinc, and in aqueous solution, which suggests that iron fortification of foods will not affect zinc absorption. Although it is possible that iron supplementation could affect mechanisms of zinc uptake and transport, studies have not found such an effect, and long-term iron supplementation is not considered to impair zinc status.

Zinc can form complexes with ligands or chelators; if the complex is readily absorbed, this can increase zinc absorption. *Edetic acid* has been found to have variable effects on zinc status depending on the ratio of edetic acid to other cations and phytate, which compete for complex formation with zinc. *Histidine* also chelates with zinc and can increase plasma zinc concentrations; however, the ratio of histidine to zinc is important because high doses of histidine may enhance the urinary excretion of zinc. *Methionine* may improve zinc absorption, although evidence is limited. Adding organic acids such as *citrate* to foods can enhance zinc absorption; zinc citrate has been used as a dietary supplement.

1. Lönnerdal B. Dietary factors influencing zinc absorption. *J Nutr* 2000; **130:** 1378S–1383S.

Human Requirements

UK and US recommended dietary intake. In the UK dietary reference values (DRV)[1] and in the USA recommended dietary allowances (RDA)[2] have been published for zinc (see p.1925 for an explanation of these terms). In the UK the reference nutrient intake (RNI) for adult males and females is 9.5 and 7.0 mg daily respectively; values are also given for infants and children of varying ages and for lactating women. The Expert Group on Vitamins and Minerals[3] have established a safe upper level (SUL) for zinc of 25 mg daily. In the USA the RDA for adults is 11 mg daily for men and 8 mg daily for women.[2] The tolerable upper intake level is 40 mg daily.

WHO recommend lower limits of the safe ranges of population mean intakes of dietary zinc for 3 categories of diets based on high, moderate, and low zinc bioavailability: values are 4.0, 6.5, and 13.1 mg dietary zinc daily for women, and 5.6, 9.4, and 18.7 mg dietary zinc daily for men, respectively.[4] They recommend an upper limit of the safe range of population mean intakes of zinc of 35 mg daily for women, and 45 mg daily for men.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf (accessed 14/11/05)
4. WHO. Zinc. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 72–104.

Uses and Administration

Zinc is an essential element of nutrition and traces are present in a wide range of foods. It is a constituent of many enzyme systems and is present in all tissues. Features of zinc deficiency include growth retardation and defects of rapidly-dividing tissues such as the skin, the immune system, and the intestinal mucosa. Water-soluble zinc salts are used as supplements to correct zinc deficiency; for example, in malabsorption syndromes, during parenteral feeding, in conditions with increased body losses (trauma, burns, and protein-losing states), and in acrodermatitis enteropathica (a rare genetic disorder characterised by severe zinc deficiency). They have been tried in the treatment of a large number of conditions that may be related to zinc deficiency.

Doses of zinc salts are usually expressed in terms of elemental zinc, and the following salts contain about 50 mg of zinc:

- zinc acetate (dihydrate) 168 mg
- zinc chloride 104 mg
- zinc citrate (trihydrate) 160 mg
- zinc gluconate 348 mg
- zinc sulfate (heptahydrate) 220 mg

The approximate number of millimoles of zinc contained in these salts are:

- 4.6 mmol in 1 g zinc acetate (dihydrate)
- 7.3 mmol in 1 g zinc chloride
- 4.8 mmol in 1 g zinc citrate (trihydrate)
- 2.2 mmol in 1 g zinc gluconate
- 3.5 mmol in 1 g zinc sulfate (heptahydrate)

In **deficiency states**, zinc is usually given orally as the sulfate, the sulfate monohydrate, or the gluconate, in doses of up to 50 mg of elemental zinc three times daily. When intravenous supplements are required, zinc chloride or zinc sulfate may be given; a suggested dose for parenteral nutrition is 6.5 mg of elemental zinc (100 micromoles) daily.

Oral zinc salts, commonly the acetate, may be used as copper absorption inhibitors in **Wilson's disease** (p.1459). The usual adult dose is 50 mg three times daily up to a maximum of five times daily. Children from 1 to 6 years may be given 25 mg twice daily; those from 6 to 16 years and with a body-weight under 57 kg are given 25 mg three times daily. Adolescents from 16 years of age, or with a body-weight of above 57 kg are given 50 mg three times daily. An effective dose in pregnant women is usually 25 mg three times daily; however, dosage is adjusted based on copper concentrations.

Zinc sulfate is used topically in a variety of skin conditions mainly for its **astringent** properties. The insoluble zinc salts, commonly the oxide (p.1621), are used similarly. A 1.2% solution of zinc acetate is used topically with erythromycin in the treatment of acne vulgaris (p.1577). Zinc sulfate is also used as an astringent in eye drops. Zinc chloride has been used for its powerful caustic and astringent properties, usually in very dilute solution, in, for example, mouthwashes. Zinc citrate has been used in preparations for oral care and as a dietary supplement.

Age-related macular degeneration. High doses of dietary supplements such as betacarotene, vitamin C, vitamin E, and zinc are being promoted for preservation of vision in the elderly but there are no data to suggest any benefit for patients who do not have age-related macular degeneration or have only mild disease and such treatment is not necessarily harmless.[1] For further details, see under Betacarotene, p.1931.

1. Anonymous. Antioxidant vitamins and zinc for macular degeneration. *Med Lett Drugs Ther* 2003; **45:** 45–46.

Common cold. Zinc salts, in the form of lozenges, have been tried in the treatment of the common cold (p.850) with variable results.[1-4] A systematic review of randomised trials found that there was no strong evidence to recommend their use.[5] Similarly, variable results have been obtained with intranasal preparations of zinc gluconate;[6-8] intranasal zinc sulfate has proven ineffective.[9]

1. Mossad SB, *et al.* Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996; **125:** 81–8.
2. Macknin ML, *et al.* Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998; **279:** 1962–7.
3. Prasad AS, *et al.* Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133:** 245–52.
4. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000; **31:** 1202–8.
5. Marshall I. Zinc for the common cold. [Withdrawn and awaiting update]. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 21/07/08).
6. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001; **33:** 1865–70.
7. Hirt M, *et al.* Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000; **79:** 778–82.
8. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *Q J Med* 2003; **96:** 35–43.
9. Belongia EA, *et al.* A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; **111:** 103–8.

Deficiency states. General references.

1. Hambidge M. Human zinc deficiency. *J Nutr* 2000; **130** (suppl): 1344S–1349S.
2. Prasad AS. Zinc deficiency: has been known of for 40 years but ignored by global health organisations. *BMJ* 2003; **326:** 409–10.
3. Shrimpton R, *et al.* Zinc deficiency: what are the most appropriate interventions? *BMJ* 2005; **330:** 347–9.
4. Mason P. Physiological and medicinal zinc. *Pharm J* 2006; **276:** 271–4.

DIAGNOSIS AND TESTING. A loss of taste acuity is a sign of zinc deficiency (see Taste Disorders, below) and this has been used as a test for the condition: patients who do not immediately perceive a strong flavour on tasting a dilute (typically 0.1 or 0.2%) solution of zinc sulfate are considered likely to benefit from supplementation. However, a study in pregnant women failed to confirm that the ability to taste such a solution was related to zinc deficiency.[1]

Authors of a small study of Japanese children with short stature evaluated body zinc clearance, and considered those patients with high clearance values but normal serum zinc concentrations to have marginal zinc deficiency.[2]

1. Mahomed K, *et al.* Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1993; **48:** 169–75.
2. Kaji M, *et al.* Studies to determine the usefulness of the zinc clearance test to diagnose marginal zinc deficiency and the effects of oral zinc supplementation for short children. *J Am Coll Nutr* 1998; **17:** 388–91.

DIARRHOEA. Chronic diarrhoea can be a sign of zinc deficiency, and diarrhoea can lead to excessive zinc losses and zinc deficiency when dietary zinc is inadequate. Zinc supplements have been shown to reduce the incidence, intensity, or duration of acute diarrhoea (p.1694) in children in developing countries.[1-5] Beneficial effects have also been seen with zinc supplementation for persistent diarrhoea.[4,5] A WHO report concluded that zinc supplementation at a dose of about 10 to 20 mg daily for 14 days is efficacious in significantly reducing the severity and duration of diarrhoea; the type of zinc salt does not appear to influence efficacy, although the best formulation should be determined to minimise adverse effects such as vomiting.[6] A further report[7] concluded that there was sufficient evidence to recommend the inclusion of zinc as adjunctive therapy to oral rehydration salts in the standard management of both dysenteric and non-dysenteric acute diarrhoea.

For a report of increased efficacy in reducing persistent diarrhoea and dysentery when zinc is used with vitamin A, see Diarrhoea, under Deficiency states, p.1973. For suggestions that zinc potentiates the effect of vitamin A, see Vitamin A deficiency, below.

1. Bhutta ZA, *et al.* Zinc Investigators' Collaborative Group. Prevention of diarrhea and pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Bhutta ZA, *et al.* Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; **72:** 1516–22.
3. Aggarwal R, *et al.* Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis. *Pediatrics* 2007; **119:** 1120–30.
4. Lukacik M, *et al.* A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. *Pediatrics* 2008; **121:** 326–36.
5. Fischer Walker CL, Black RE. Micronutrients and diarrheal disease. *Clin Infect Dis* 2007; **45** (suppl 1): S73–S77.
6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *J Health Popul Nutr* 2001; **19:** 338–46.
7. Robberstad B, *et al.* Cost-effectiveness of zinc as adjunct therapy for acute childhood diarrhoea in developing countries. *Bull WHO* 2004; **82:** 523–31.

GROWTH RETARDATION. Growth retardation in a group of short Japanese children without endocrine abnormalities was found to be associated with mild to moderate zinc deficiency; supplementation with oral zinc sulfate 5 mg/kg daily over 6 months resulted in an improvement in growth velocity despite unchanged growth hormone production.[1] Similarly, supplementation with 10 mg zinc daily for 6 days of each week, for 6 months, increased the growth rate of stunted Ethiopian infants; weight also increased in both stunted and non-stunted children, and the authors commented that these effects were at least partly due to improvements in appetite, and reduced morbidity from infection.[2] Results from a meta-analysis of these 2 studies and 31 others indicated that zinc supplementation resulted in a highly significant increase in both linear growth and weight gain of prepubertal children; weight-for-height index was not affected. Significant increases in serum zinc concentrations were also noted with supplementation, but additional studies were considered necessary in order to determine whether mean serum zinc concentration could accurately predict response to supplementation.[3]

1. Nakamura T, *et al.* Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. *J Pediatr* 1993; **123:** 65–9.
2. Umeta M, *et al.* Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet* 2000; **355:** 2021–6.
3. Brown KH, *et al.* Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; **75:** 1062–71.

PNEUMONIA. A pooled analysis[1] of 10 studies performed in developing countries found that zinc supplementation reduced the incidence of pneumonia in children by 41%. A randomised study in Bangladesh, in 270 children aged 2 to 23 months, found that 20 mg daily of elemental zinc, given by mouth and adjuvant to standard antimicrobial therapy, accelerated recovery from pneumonia when compared with placebo; children aged 12 months or older resolved their respiratory illness earlier than younger infants.[2] Another study in Bangladesh[3], involving 1621 children 2 to 12 months old, found that prophylaxis with 70 mg of oral zinc acetate [about 20 mg of zinc] given weekly reduced the incidence of pneumonia compared with placebo and also reduced subsequent

pneumonia-related mortality; a small reduction in the incidence of diarrhoea was also seen.

1. Bhutta ZA, *et al.* Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatr* 1999; **135:** 689–97.
2. Brooks WA, *et al.* Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. *Lancet* 2004; **363:** 1683–8.
3. Brooks WA, *et al.* Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. *Lancet* 2005; **366:** 999–1004.

PREGNANCY. Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45 mg daily) during pregnancy may have beneficial effects on fetal growth and development, and lead to improved pregnancy outcomes.[1] A controlled study in Peru found that addition of oral zinc (25 mg of zinc daily as zinc sulfate) to iron and folate supplementation improved fetal bone growth, as measured by femur length.[2] A systematic review[3] concluded that, while zinc supplementation during pregnancy appears to reduce preterm delivery, there was no convincing evidence that it resulted in other useful benefits. Since the association with preterm birth might reflect poor nutrition, improvement in the overall nutritional status of impoverished populations would be more beneficial than zinc supplementation in isolation.

1. Favier M, Hininger-Favier I. Zinc et grossesse. *Gynecol Obstet Fertil* 2005; **33:** 253–8.
2. Merialdi M, *et al.* Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *Am J Clin Nutr* 2004; **79:** 826–30.
3. Mahomed K, *et al.* Zinc supplementation for improving pregnancy and infant outcome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 05/03/08).

TASTE DISORDERS. Zinc appears to be effective for the treatment of taste disturbances (p.977) associated with zinc deficiency but there is insufficient evidence to determine its efficacy for taste dysfunction secondary to conditions that do not involve low serum zinc concentrations.[1] Zinc picolinate was found to significantly improve objective measurement of taste when compared with placebo, both in patients with zinc deficiency and in those with idiopathic taste disorders (and normal serum zinc concentrations); there were no differences in subjective assessment of taste.[2] A later study[3] also found oral zinc gluconate 140 mg daily [about 20 mg of zinc] to be of benefit in idiopathic dysgeusia.

1. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
2. Sakai F, *et al.* Double-blind, placebo-controlled trial of zinc picolinate for taste disorders. *Acta Otolaryngol* 2002; (suppl 546): 129–33.
3. Heckmann SM, *et al.* Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. *J Dent Res* 2005; **84:** 35–8. Correction. *ibid.*; 382.

Vitamin A deficiency. It has been proposed[1] that the inconsistent effects on morbidity of vitamin A supplementation (see Diarrhoea, under Deficiency States, p.1973) may be due to co-existing micronutrient deficiencies, such as zinc deficiency, that affect the bioavailability of vitamin A. The authors found combined zinc and vitamin A supplementation to be more effective in reducing persistent diarrhoea and dysentery than either zinc or vitamin A alone. There is also some suggestion that zinc may potentiate the effects of vitamin A in the treatment of night blindness,[2] but only in those patients already deficient in zinc. A study in Bangladesh[3] found that the proportional improvement in vitamin A status in vitamin A-deficient children was larger in those given zinc with vitamin A than in those given vitamin A or zinc alone, suggesting a synergistic effect. Similarly, a study in Indonesia[4] of supplementation in pregnant women found that betacarotene with zinc, but not betacarotene or zinc alone, improved vitamin A status in both mothers and infants at 6 months postpartum; the authors suggested that zinc may have a specific role in the conversion of betacarotene to retinol.

1. Rahman MM, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001; **323:** 314–18.
2. Christian P, *et al.* Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *Am J Clin Nutr* 2001; **73:** 1045–51.
3. Rahman MM, *et al.* Synergistic effect of zinc and vitamin A on the biochemical indexes of vitamin A nutrition in children. *Am J Clin Nutr* 2002; **75:** 92–8.
4. Dijkhuizen MA, *et al.* Zinc plus β-carotene supplementation of pregnant women is superior to β-carotene supplementation alone in improving vitamin A status in both mothers and infants. *Am J Clin Nutr* 2004; **80:** 1299–1307.

Wilson's disease. References.

1. Anderson LA, *et al.* Zinc acetate treatment in Wilson's disease. *Ann Pharmacother* 1998; **32:** 78–87.
2. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc: XV long-term follow-up studies. *J Lab Clin Med* 1998; **132:** 264–78.
3. Brewer GJ, *et al.* Treatment of Wilson's disease with zinc: XVII: treatment during pregnancy. *Hepatology* 2000; **31:** 364–70.
4. Brewer GJ. Zinc acetate for the treatment of Wilson's disease. *Expert Opin Pharmacother* 2001; **2:** 1473–7.

Preparations

BP 2008: Erythromycin and Zinc Acetate Lotion; Zinc Sulphate Eye Drops; Zinc Sulphate Lotion;
USP 31: Zinc Chloride Injection; Zinc Sulfate Injection; Zinc Sulfate Ophthalmic Solution; Zinc Sulfate Oral Solution; Zinc Sulfate Tablets; Zinc Sulfide Topical Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Galzin; Z-Kraft†; ***Austral.:*** Bioglan Zinc Chelate; Zincaps; ***Austria:*** Zinkamin†; ***Braz.:*** Zincopan; ZN Xampu; ***Canad.:*** Anu-Aide†; Anusol; Anuzinc; Egozinc; Rivasol; ***Chile:*** Num-Zit; ***Cz.:*** Wilzin; Zincteral; Zinek-AlO†; Zinkorotat-POS; ***Fr.:*** Effizinc; Rubozinc; Wilzin; Zymizinc†; ***Ger.:*** Biolectra Zink; Biosan Zink†; Cefazink; Curazink; Nefro-Zinc; Ophtopur-Z; Solvezink†; Unizink; Virudermin; Vitazink; Wilzin; Zink beta; Zink Verla; Zink-D Longoral; Zink-Ratiopharm; Zink-Sandoz; Zinkamin; Zinkaspart; Zinkbrause; Zinkit; Zinkorot; Zinkotase; ***Hong Kong:*** Egozinc; Eye Glo Relief; Zincaps; ***Irl.:*** Solvazinc; ***Israel:*** Avazinc; Zincol; ***Ital.:*** Pontefix; Troca Flu Rino; Wilzin; ***Mex.:*** Tersaken†; Unguento del Bebe; Z-Crim; Zn-Fusin†; ***Neth.:*** Wilzin; ***Norw.:*** Solvezink; ***NZ:*** Elemental Zinc†; Zincaps; ***Philipp.:*** Immuzinc; Prozinc; Zinbee; ***Pol.:*** Wilzin; Zincas; Zincteral; ***Port.:*** Wilzin; ***Spain:*** Wilzin; ***Swed.:*** Solvezink; ***Switz.:*** Collazin; Virudermin; ***Thai.:*** Zincaps; Zinctab†; ***Turk.:*** Zinco; ***UK:*** Solvazinc; Tartar Control Listerine; Wilzin; Zincomed; Zincosol; ***USA:*** Dermadrox; Galzin; Halls Zinc Defense; Ivy Dry; Orazinc; Verazinc; Zinca-Pak; Zincate.

Multi-ingredient: ***Arg.:*** Caladryl Incoloro; Callicida; Citrovita; Clean-AC; Cleanance; Crema de Ordene; Crema Para Paspaduras; Dermalibour; Kelual Zinc; Lacto-Cev Zn; Lactocrem Bebe; Lagrimas de Santa Lucia†; Litiofarm†; Megaplus; Negacne; Ninderm; Redoxon Doble Accion; Sigma CE; Sigmace Plus; Zineryt; ***Austral.:*** Antioxidant Forte Tablets; Antioxidant Tablets; APR Cream†; Beta A-C; Bioglan Joint Mobility; Bioglan The Blue One; Bioglan Zn-A-C; Caprilate; Cold and Flu Relief†; Cold Sore Relief†; Echinacea 4000; Echinacea ACE + Zinc; Echinacea Complex; Extralife Eye-Care; Extralife Flow-Care; Galium Complex†; Goodnight Formula†; In A Wink†; Lifechange Mens Complex with Saw Palmetto†; Lifesystem Herbal Plus Formula 8 Echinacea†; Logicin Natural Lozenges†; Odourless Garlic†; Proyeast†; Redoxon Double Strength; Serenoa Complex†; Strepsils Zinc Cold Relief; Trifolium Complex†; Urapro†; Visine Allergy†; Zinc + C250†; Zinc C Plus†; Zinc Plus; Zinc Supplement†; Zinc Zenith; Zincfrin; Zinvit; Zinvit C; Zinvit G; ***Austria:*** Efalith; Lipactin; Ophtaguttal; Zeller-Augenwasser; ***Belg.:*** Efalith; Lipactin; Redoxon + Zink; Zincfrin; Zincfrin Antihistaminicum†; Zineryt; ***Braz.:*** Antiseptin†; Babymed; Belagin; Cariderm†; Cebion Zinco; Colirio Legrand; Colirio Moura Brasil; Colirio Teuto; Fluo-Vaso; Kalloplast†; Maxibell; Mirabel; Mirorroidin†; Redoxon Zinco; Sensibaby; Stilux; Suavederm; Visiplex; Visolon; Visual†; Zincolok; ***Canad.:*** Anodan-HC; Anugesic-HC; Anusol Plus; Anusol-HC; Anuzinc HC; Anuzinc HC Plus; Anuzinc Plus; Clear Eyes Allergy; Egozinc-HC; Hemorrhoid Ointment; Lipactin; Listerine Antiseptic Tartar Control; One A Day Cold Season†; Onguent Hemorrhoidal; Orajel Mouth Sore Medicine; Polysporin Itch Relief; Proctodan-HC; ProstGard†; ratio-Hemcort-HC; Rectogel; Rectogel HC; Rivasol HC; Visine Allergy; Zinc Plus; Zincfrin; Zincfrin-A; ***Chile:*** Agua Sulfatada Picrica; Astrijesan; Caladryl Clear; Cicalfate; Clean-AC; Cleanance; Deltisan; Gingilacer†; Oculosan; Orajel Compuesto†; Oralfresh Citrus; Orthokin; Ortodent†; Pomada Antihemorroidal†; Primacy C+AHA†; Sebium AKN; Sebium H2O; ***Cz.:*** Acne Lotio†; Curiosin†; Osteocare; Redoxon Double Action; Zineryt; ***Denm.:*** Zincfrin; ***Fin.:*** Lipactin; Wicnelact; Zincfrin-A†; Zincfrin†; ***Fr.:*** Aftagel; Atoderm moussant; Cicalfate; Cicaplast; Clean-AC; Cleanance; Cleanance K; Cu-Zn; Cystel Shampooing Antiseborrheique†; Cysti-Z†; D'Contract; Dermalibour; Dermo-Sulfuryl; Evosebor Li-Zn; Kelual Zinc; Keralac Plus†; Purif-Ac Emulsion; Purif-Ac Gel; Ramet Dalibour; Ramet Pain; Ruboderm Plus; Sebium AKN; Seborheane; Septalibour†; Serozinc; Supro; YSE; YSE Glutamique; Zeniac LP†; Zeniac†; ***Ger.:*** Algosteril Trionic†; Efadermin; Gehwol Nagelpilz†; Lipactin; Oculosan N; Zincfrin; Zineryt; ***Gr.:*** Oculosan; Zabysept; ***Hong Kong:*** Aderma Dermalibour†; Hemcort HC†; Listerine Tartar Control; Nazin; Oculosan; Osteocare; Redoxon Double Action; Visine AC; ***Hung.:*** Osteocare; Vition; Zineryt; ***India:*** Andre; Aristrol Forte†; Cofol Z; Elferri-Z; Fecontin-Z; Fefol-Z; Ferrochelate-Z; Globac-Z; JP Tone-TR; Livogen-Z; Mumfer-Z†; New Eye Lotion; Ocurest-Z; Zad-G; Zinco Sulpha; ***Indon.:*** Artriox; Biostrum; Climadan; Enerbex; Ilefrin; Imboost; Imboost Force; Imudator; Indofrin; Indofrin-A; Isotic Frizin; Oculosan; Osteocare; Proza; Redoxon Double Action; Soprost; Stacare; StarMuno; Zincopto; ***Irl.:*** Efalith; Redoxon Double Action; Zineryt; ***Israel:*** Hemo; Visine AC; ***Ital.:*** Acnesan†; Bagno Oculare†; Cuprosodio; Cuprosodio Plus; Emmenoiasi; Forbrand; Formedico; Ginsana Ton; Indaco; Inflamase; Influ-Zinc; Influ-Zinc Gola; Listerine Tartar Control; Meziv†; Novostatin; Periogard Plus; Zinc-Imizol; Zincometil; Zineryt; ***Malaysia:*** Adult Citrex; Oculosan†; Zincfrin†; ***Mex.:*** Afazol Z; Caladryl Clear; Dalidome; Daribur; Exastrin; Gripaleta†; Micostatin Baby; Periodentyl; Soyaloid Apruri; Tokolirio; Unguento Cruz; Unguento de la Madre; Unguento Sulfatiazol Rojtier; Z Frin; Zincfrin; Zincfrin-A; ***Neth.:*** Zineryt; ***NZ:*** Clear Eyes ACR†; Listerine Tartar Control; Redoxon Double Action; Strepsils Zinc Defence; Zincfrin; ***Philipp.:*** Bo-D-Fense; Listerine Tartar Control; Oculosan; Osteocare; ***Pol.:*** Biherpan; Cincol; Hemcort HC; Naturapia Prostata; Oculosan; Zincuprin; Zineryt; ***Port.:*** Bioclin Sebo Care†; Kemphor; Oralbiotico; Oratol; Zineryt; ***Rus.:*** Anusol (Анузол); Relief Ultra (Релиф Ультра); Zineryt (Зинерит); ***S.Afr.:*** Nazene Z; Oculoforte†; Oculosan; Tartar Control Listerine Antiseptic; Zincfrin-A; Zineryt; ***Singapore:*** Listerine Tartar Control; New Daigaku†; Proza; Redoxon All Day Defence; Redoxon Double Action; Vita Calmag Zn†; ***Spain:*** Buco Regis; Cloram Zinc; Coliriocilina Adren Astr; Odamida; Odontocromil c Sulfamida†; Zincfrin†; Zineryt; ***Swed.:*** Mezinc; Zincfrin; ***Switz.:*** Acne Lotion; Collypan; Eau pour les yeux; Efalith; Hima-Pasta; Lipactin; Oculosan; Redoxon + Zinc; ***Thai.:*** Bio-Selenium Zinc; Oculosan; Opplin†; Visotone; ***Turk.:*** Osteocare; Zinco C; ***UK:*** Brushtox; Dispello; Flavo-Zinc; Lypsyl Cold Sore Gel; Osteocare; Redoxon Double Action; Se-Power; Strepsils Zinc Defence†; Vicks Vital†; Zineryt; ***USA:*** Amerigel; Anti-Itch; Benadryl Itch; Better Prostate†; Caladryl Clear; Cholesterol Support; Clear Eyes Seasonal Relief; Dermadrox; Dermasept Antifungal; Fosteum; Gets-It; Nasal-Ease; Orajel Mouth Aid; Prostate Support; Sucrets Defense Kids Formula; Sulpho-Lac; Super Ivy Dry; VasoClear A; Visine Allergy Relief; Wound Cleanser; Ze Caps†; Zincfrin; ***Venez.:*** Calasyl Transparente; Dermagran; Sebium AKN; Terace Zinc.

becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women, and for all women younger than 18 years of age.[2,3] It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators,[1,3] mifepristone, or a prostaglandin such as gemeprost or misoprostol.[1-3] Various drugs, used alone and in combination, have been tried for *medical termination* of pregnancy. Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring about successful termination when used alone, but the high doses required can cause significant adverse effects.[4-6] The most commonly used prostaglandins are gemeprost and misoprostol;[3,4] others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects.[3] The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.[3-5,7] The antimetabolite methotrexate has also been used with misoprostol, but it has a delayed effect and the time from induction to abortion can be several days or weeks.[4,5] Other methods that have been used for termination of pregnancy, particularly in the second trimester, include intra-amniotic use of dinoprost, hypertonic sodium chloride, or hyperosmolar urea augmented with oxytocin, carboprost, or dinoprost.[1]

Uterine cramping and bleeding are associated with both surgical and medical termination processes. Surgical termination may be carried out under conscious sedation,[1,2] local anaesthesia using paracervical block,[1-3] or general anaesthesia.[2] Analgesia requirements in medical termination may be higher in younger women, nulliparous women, and those with longer gestations.[3,4] Analgesics such as paracetamol, NSAIDs, and codeine are commonly used.[6] Generally, bleeding lasts longer after medical termination than after vacuum aspiration.[6] With medical termination using mifepristone plus a prostaglandin, bleeding is initially heavy but gradually diminishes over about 2 weeks, although minor bleeding can continue for longer.[1,6]

Factors influencing the choice of method for termination include the stage of gestation, availability of surgical services and abortifacient drugs, and the woman's preference. The most common approaches are outlined below.

- In the early first trimester (up to 49 days) a medical method, using mifepristone followed by a prostaglandin, is preferred because the failure rate is higher with vacuum aspiration.[2,6] Methotrexate followed by a prostaglandin is an alternative at this early stage,[1,5] but expulsion can take several days or weeks.[4] Either a surgical or medical method can be used between 49 and 63 days of gestation. However, oral misoprostol for medical termination becomes less effective as gestation progresses[4,5] so a vaginal prostaglandin is preferred.[2,5,6]
- In the late first trimester (up to 13 weeks) a surgical or medical method may be used. After 9 or 10 weeks of gestation, cervical preparation is used before surgical procedures and multiple doses of prostaglandin may be needed to achieve medical termination.[2]
- In mid-trimester termination (13 to 24 weeks) a surgical or medical method may be used. Cervical preparation is essential before surgical termination and multiple doses of prostaglandin will generally be required for medical termination.[2,3]

Some of the methods used for termination of pregnancy are also used to hasten miscarriage after pregnancy failure or early fetal death. Surgical evacuation is effective but associated with a higher risk of infection than expectant management.[8] Vaginal misoprostol can also hasten miscarriage, but oral use is less effective.[9] For the management of intra-uterine fetal death in later pregnancy, see Labour Induction and Augmentation, above.

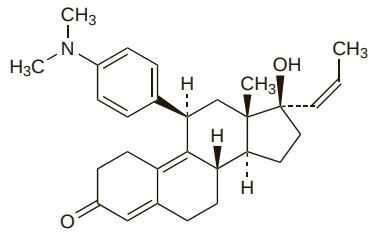
1. Stubblefield PG, *et al.* Methods for induced abortion. *Obstet Gynecol* 2004; **104:** 174–85.
2. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7 (issued September 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/induced_abortionfull.pdf (accessed 30/06/08)
3. Lalitkumar S, *et al.* Mid-trimester induced abortion: a review. *Hum Reprod Update* 2007; **13:** 37–52.
4. Hamoda H, Flett GMM. Medical termination of pregnancy in the early first trimester. *J Fam Plann Reprod Health Care* 2005; **31:** 10–14.
5. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Medical management of abortion (ACOG practice bulletin number 67, issued October 2005). *Obstet Gynecol* 2005; **106:** 871–82.
6. WHO. Frequently asked clinical questions about medical abortion (2006). Available at: http://www.who.int/reproductive-health/publications/medical_abortion/faq.pdf (accessed 30/06/08)
7. Kulier R, *et al.* Medical methods for first trimester abortion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 30/06/08).
8. Nanda K, *et al.* Expectant care versus surgical treatment for miscarriage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 30/06/08).
9. Neilson JP, *et al.* Medical treatment for early fetal death (less than 24 weeks). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 30/06/08).

Aglepristone *(rINN)*

Aglepristona; Aglépristone; Aglepristonum; RU-46534. 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-[(*Z*)-propenyl]estra-4,9-dien-3-one.

Аглепристон

$C_{29}H_{37}NO_2$ = 431.6.
CAS — 124478-60-0.
ATC Vet — QG03XB90.



Profile

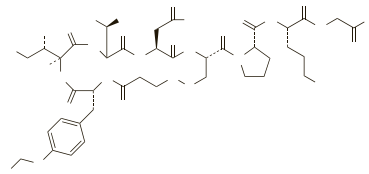
Aglepristone has antiprogestogenic activity and is used in veterinary medicine as an abortifacient in *dogs*.

Atosiban *(BAN, USAN, rINN)*

Atosibaani; Atosibanum; ORF-22164; RWJ-22164. 1-(3-Mercaptopropionic acid)-2-[3-(*p*-ethoxyphenyl)-D-alanine]-4-L-threonine-8-L-ornithineoxytocin; [1-(3-Sulfanylpropanoyl),2-(4-*O*-ethyltyrosine),4-L-threonine-8-L-ornithine]oxytocin.

Атозибан

$C_{43}H_{67}N_{11}O_{12}S_2$ = 994.2.
CAS — 90779-69-4.
ATC — G02CX01.
ATC Vet — QG02CX01.



Adverse Effects and Precautions

Adverse effects reported in women receiving atosiban for premature labour include nausea and vomiting, headache, dizziness, flushes, tachycardia, hypotension, hyperglycaemia, and injection site reactions. Atosiban should not be used where continuation of pregnancy is hazardous to mother or fetus, including where gestational age is below 24 or over 33 weeks, in eclampsia or severe pre-eclampsia, intra-uterine growth retardation and abnormal fetal heart rate, suspected intra-uterine infection, placenta praevia, or abruptio placentae. Monitoring of uterine contractions and fetal heart rate is recommended during use, and blood loss should be monitored after delivery.

Although there has been some concern about fetal exposure, licensed product information states that no specific adverse effects on the newborn have been reported.

Pharmacokinetics

In women in premature labour, atosiban reaches steady-state plasma concentrations within one hour of the start of infusion, and has a terminal half-life of 1.7 hours after stopping infusion. Atosiban is 46 to 48% bound to plasma proteins, and crosses the placenta. It is metabolised to an active metabolite, which is excreted in the urine; both atosiban and this metabolite are distributed into breast milk.

Uses and Administration

Atosiban is a peptide analogue of oxytocin (p.2015) but with oxytocin antagonist properties. It is used as a tocolytic in the management of premature labour (p.2003). Atosiban is given intravenously as the acetate, but doses are expressed in terms of the base. An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.

Premature labour. References.

1. Romero R, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000; **182:** 1173–83.
2. Valenzuela GJ, *et al.* Maintenance treatment of preterm labor with the oxytocin antagonist atosiban: the Atosiban PTL-098 Study Group. *Am J Obstet Gynecol* 2000; **182:** 1184–90.
3. Moutquin JM, *et al.* Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000; **182:** 1191–9.
4. The Worldwide Atosiban versus Beta-agonists Study Group. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. *Br J Obstet Gynaecol* 2001; **108:** 133–42.
5. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor: a randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001; **80:** 413–22.
6. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 177–85.
7. Coomarasamy A, *et al.* Oxytocin antagonists for tocolysis in preterm labour—a systematic review. *Med Sci Monit* 2002; **8:** RA268–73.
8. Tsatsaris V, *et al.* Atosiban for preterm labour. *Drugs* 2004; **64:** 375–82.
9. Husslein P, *et al.* Atosiban versus usual care for the management of preterm labor. *J Perinat Med* 2007; **35:** 305–13.

Preparations

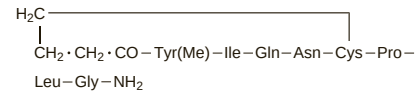
Proprietary Preparations (details are given in Part 3)
Arg.: Tractocile; ***Austria:*** Tractocile; ***Belg.:*** Tractocile; ***Braz.:*** Tractocile†; ***Cz.:*** Tractocile; ***Denm.:*** Tractocile; ***Fin.:*** Tractocile; ***Fr.:*** Tractocile; ***Ger.:*** Tractocile; ***Gr.:*** Tractocile; ***Hong Kong:*** Tractocile; ***Hung.:*** Tractocile; ***Irl.:*** Tractocile; ***Ital.:*** Tractocile; ***Malaysia:*** Tractocile; ***Mex.:*** Tractocile; ***Neth.:*** Tractocile; ***Norw.:*** Tractocile; ***NZ:*** Tractocile; ***Pol.:*** Tractocile; ***Port.:*** Tractocile; ***S.Afr.:*** Tractocile; ***Spain:*** Tractocile; ***Swed.:*** Tractocile; ***Switz.:*** Tractocile; ***UK:*** Tractocile.

Carbetocin *(BAN, rINN)*

Carbetocina; Carbétocine; Carbetocinum; Karbetocin; Karbetosiini. 2,1-Desamino-4,1-desthio-*O*^{4,2}-methyl[1-homocysteine]-oxytocin; 1-Butyric acid-2-[3-(*p*-methoxyphenyl)-L-alanine]oxytocin.

Карбетоцин

$C_{45}H_{69}N_{11}O_{12}S$ = 988.2.
CAS — 37025-55-1.
ATC — H01BB03.
ATC Vet — QH01BB03.



Adverse Effects and Precautions

Carbetocin has similar adverse effects and precautions to those associated with oxytocin when it is used after caesarean section (see p.2015). However, carbetocin should not be used at any stage of labour before delivery of the infant because its effects on the uterus last for several hours.

Breast feeding. In 5 women who were 7 to 14 weeks postpartum, carbetocin was measured in the breast milk within 90 minutes of a single 70-microgram intramuscular dose.[1] The ratio of milk to plasma concentrations was low, suggesting that very little carbetocin was distributed into breast milk. Licensed UK product information states that no significant effects on milk ejection were reported during clinical studies, and that any carbetocin ingested by a breast-fed infant would probably be degraded by enzymes in the gastrointestinal tract. The American Academy of Pediatrics considers that the use of carbetocin is usually compatible with breast feeding.[2]

1. Silcox J, *et al.* Transfer of carbetocin into human breast milk. *Obstet Gynecol* 1993; **82:** 456–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 30/06/08)