Pharmacokinetics

Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability of about 12% due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to a number of active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile.

◊ Reviews.

1. Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; **42:** 1141–60.

Uses and Administration

Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (or statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394). It is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169), including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III). Atorvastatin can be effective as adjunctive therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. It is also used for primary and secondary prophylaxis of cardiovascular events (see Cardiovascular Risk Reduction, p.1164) in patients with multiple risk factors, including diabetes mellitus.

Atorvastatin is given orally as the calcium salt although doses are expressed in terms of the base; 10.82 mg of atorvastatin calcium trihydrate is equivalent to 10 mg of base. The usual initial dose is 10 to 20 mg of atorvastatin once daily; an initial dose of 40 mg daily may be used in patients who require a large reduction in LDL-cholesterol. The dose may be adjusted at intervals of 4 weeks up to a maximum of 80 mg daily.

For patients taking drugs that interact with atorvastatin, dose reduction is advised as follows:

- patients taking *ciclosporin*, maximum dose 10 mg once daily
- patients taking *clarithromycin*, initial dose 10 mg once daily and maximum dose 20 mg once daily
- patients taking *itraconazole*, initial dose 10 mg once daily and maximum dose 40 mg once daily
- patients taking *ritonavir-boosted lopinavir* or *ritonavir-boosted saquinavir*, doses above 20 mg once daily should be used with caution

For the use of atorvastatin in children and adolescents, see below.

◊ General reviews.

1. Lea AP, McTavish D. Atorvastatin: a review of its pharmacology and therapeutic potential in the management of hyperlipidaemias. *Drugs* 1997; **53:** 828–47.
2. Malinowski JM. Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. *Am J Health-Syst Pharm* 1998; **55:** 2253–67.
3. Malhotra HS, Goa KL. Atorvastatin: an updated review of its pharmacological properties and use in dyslipidaemia. *Drugs* 2001; **61:** 1835–81.
4. Croom KF, Plosker GL. Atorvastatin: a review of its use in the primary prevention of cardiovascular events in patients with type 2 diabetes mellitus. *Drugs* 2005; **65:** 137–52.
5. Poli A. Atorvastatin: pharmacological characteristics and lipid-lowering effects. *Drugs* 2007; **67** (suppl 1): 3–15.
6. Bybee KA, *et al.* Cumulative clinical trial data on atorvastatin for reducing cardiovascular events: the clinical impact of atorvastatin. *Curr Med Res Opin* 2008; **24:** 1217–29.

Administration in children. In children and adolescents aged 10 to 17 years with hypercholesterolaemia or combined (mixed) hyperlipidaemia, atorvastatin is licensed for use orally in an initial dose of 10 mg once daily, adjusted if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg once daily. A 6-month study[1] with this dose regimen in children with familial or severe hypercholesterolaemia found that atorvastatin was both safe and effective. Atorvastatin has also been used in children with hyperlipidaemia associated with renal[2] or heart[3] transplantation.

1. McCrindle BW, *et al.* Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003; **143:** 74–80.
2. Argent E, *et al.* Atorvastatin treatment for hyperlipidemia in pediatric renal transplant recipients. *Pediatr Transplant* 2003; **7:** 38–42.
3. Chin C, *et al.* Efficacy and safety of atorvastatin after pediatric heart transplantation. *J Heart Lung Transplant* 2002; **21:** 1213–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ampliar; Atarva; Ateroclar; Atorvastan; Finlipol; Liparex; Lipibec; Lipifen; Lipitor; Lipocambi; Lipofin; Liponorm; Lipostop; Lipovastinklonal; Normalip; Plan; Tialipol; Torivas; Vastina; Zarator; ***Austral.:*** Lipitor; ***Austria:*** Sortis; ***Belg.:*** Lipitor; ***Braz.:*** Citalor; Lipitor; ***Canad.:*** Lipitor; ***Chile:*** Atenfar; Atorlip; Dislipor; Hipolixan; Lipitor; Lipotropic; Lipox; Lowden; Zarator; Zurinel; ***Cz.:*** Atogal; Atoris; Atorpharm; Bisatum; Sortis; Torvacard; Triglyx; Tulip; Vaston; ***Denm.:*** Zarator; ***Fin.:*** Lipitor; ***Fr.:*** Tahor; ***Ger.:*** Sortis; ***Gr.:*** Altoram; Antorcin; Arvastatil; Ator-Chol; Atorgon; Atorolnga; Atorstat; Atorval; Atorvanox; Atorvin; Atrost; Atrosterol; Atrovita; Biger; Delipost; Holisten; Lipigan; Lipitor; Lipizem; Lipodial; Lipostatin; Lipovast; Lorvaten; Rotova; Torvastin; Vastazor; Xanator; Zarator; ***Hong Kong:*** Lipitor; ***Hung.:*** Atoris; Atorva; Atorvox; Hypolip; Liprimar; Sortis; Torvacard; ***India:*** Atorlip; Atorva; Attor; Liporest; X'tor; ***Indon.:*** Atorsan; Lipitor; ***Irl.:*** Lipitor; ***Israel:*** Lipitor; Torid; ***Ital.:*** Lipitor†; Torvast; Totalip; Xarator†; ***Jpn:*** Lipitor; ***Malaysia:*** Lipitor; Storvas; ***Mex.:*** Lipitor; ***Neth.:*** Cardyl; Lipitor; Prevencor; Zarator; ***Norw.:*** Lipitor; ***NZ:*** Lipitor; ***Philipp.:*** Lipitor; ***Pol.:*** Atoris; Atrox; Sortis; Torvacard; Tulip; ***Port.:*** Sortis; Zarator; ***Rus.:*** Atomax (Атомакс); Atoris (Аторис); Liprimar (Липримар); Liptonorm (Липтонорм); Torvacard (Торвакард); Tulip (Тулип); ***S.Afr.:*** Lipitor; ***Singapore:*** Lipitor; ***Spain:*** Cardyl; Prevencor; Zarator; ***Swed.:*** Lipitor; ***Switz.:*** Sortis; ***Thai.:*** Lipitor; ***Turk.:*** Ator; Kolestor; Lipitaksin; Lipitor; Saphire; Tarden; ***UK:*** Lipitor; ***USA:*** CTR; Lipitor; ***Venez.:*** Atovarol; Glustar; Lipitor; Tarimyl.

Multi-ingredient: ***Arg.:*** Ampliar Duo; Ateroclar Duo; Hipertensal Combi; Liparex Duo; Lipibec Duo; Lipoarteriosan; Liponorm Duo; Torimibe; ***Austral.:*** Caduet; ***Braz.:*** Caduet; ***Chile:*** Caduet; ***Cz.:*** Caduet; ***Fr.:*** Caduet; ***Hung.:*** Caduet; ***India:*** Zetitor†; ***Malaysia:*** Caduet; ***Mex.:*** Caduet; ***Philipp.:*** Envacar; ***Port.:*** Caduet; ***S.Afr.:*** Caduet; ***Singapore:*** Caduet; ***USA:*** Caduet; ***Venez.:*** Caduet.

Atropine *(BAN)*

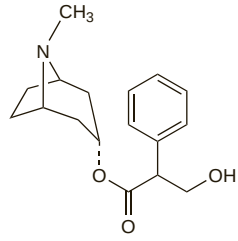
Atropiini; Atropin; Atropina; Atropinas; Atropinum; (±)-Hyoscyamine. (1*R*,3*r*,5*S*,8*r*)-Tropan-3-yl (*RS*)-tropate.

$C_{17}H_{23}NO_3$ = 289.4.

CAS — 51-55-8.

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.



Description. Atropine is an alkaloid that may be obtained from solanaceous plants, or prepared by synthesis.

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

Ph. Eur. 6.2 (Atropine). A white or almost white, crystalline powder or colourless crystals. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Atropine). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 460 of water, 1 in 90 of water at 80°, 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 25 of ether; soluble in glycerol. Its saturated solution in water is alkaline to phenolphthalein. Store in airtight containers. Protect from light.

Atropine Methobromide *(BANM)*

Atropina, metilbromuro de; Atropine Methylbromide; Methylatropine Bromide; Méthylatropine, bromure de; Methylatropini bromidum; Methylatropinii Bromidum; Methylatropinium Bromatum; Methylatropinium-bromid; Metilatropin-bromid; Metilatropino bromidas; Metylatropinbromid; Metyyliatropiinibromidi; Mydriasine. (1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium bromide.

$C_{18}H_{26}BrNO_3$ = 384.3.

CAS — 2870-71-5.

ATC — A03BA01.

ATC Vet — QA03BA01.

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

Ph. Eur. 6.2 (Methylatropine Bromide; Atropine Methobromide BP 2008). Colourless crystals or a white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

Atropine Methonitrate *(BANM, rINN)*

Atrop. Methonit.; Atropiinimetonitraatti; Atropine, Méthonitrate d'; Atropini Methonitras; Atropinmetonitrat; Methylatropine Nitrate *(USAN)*; Méthylatropine, nitrate de; Methylatropini nitras; Methylatropinii Nitras; Methylatropinium nitrát; Metilatropin-nitrát; Metilatropino nitratas; Metilnitrato de atropina; Metonitrato de atropina; Metylatropinnitrat; Metyyliatropiininitraatti. (1*R*,3*r*,5*S*)-8-Methyl-3-[(±)-tropoyloxy]tropanium nitrate.

Атропина Метонитрат

$C_{18}H_{26}N_2O_6$ = 366.4.

CAS — 52-88-0.

ATC — A03BB02.

ATC Vet — QA03BB02.

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

Ph. Eur. 6.2 (Methylatropine Nitrate; Atropine Methonitrate BP 2008). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. Protect from light.

Stability. Aqueous solutions of atropine methonitrate are unstable; stability is enhanced in acid solutions of pH below 6.

Atropine Sulfate

Atrop. Sulph.; Atropiinisulfaatti; Atropin Sülfat; Atropina, sulfato de; Atropine, sulfate d'; Atropine Sulphate *(BANM)*; Atropini sulfas; Atropini Sulfas Monohydricus; Atropino sulfatas; Atropinsulfat; Atropin-sulfát monohydrát; Atropin-szulfát; Atropiny siarczan.

$(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$ = 694.8.

CAS — 55-48-1 (anhydrous atropine sulfate); 5908-99-6 (atropine sulfate monohydrate).

ATC — A03BA01; S01FA01.

ATC Vet — QA03BA01; QS01FA01.

NOTE. Compounded preparations of atropine sulfate may be represented by the following names:

- Co-phenotrope (*BAN*)—atropine sulfate 1 part and diphenoxylate hydrochloride 100 parts (w/w).
  ATR is a code approved by the BP 2008 for use on single unit dose eye drops containing atropine sulfate where the individual container may be too small to bear all the appropriate labelling information.

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

Ph. Eur. 6.2 (Atropine Sulphate). A white or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of 4.5 to 6.2. Protect from light.

USP 31 (Atropine Sulfate). Odourless, colourless crystals or white crystalline powder. It effloresces in dry air. Soluble 1 in 0.5 of water, 1 in 2.5 of boiling water, 1 in 5 of alcohol, and 1 in 2.5 of glycerol. Store in airtight containers.

Incompatibility. Incompatibility between atropine sulfate and hydroxybenzoate preservatives has been seen,[1] resulting in a total loss of the atropine in 2 to 3 weeks.

1. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; **230:** 481.

Adverse Effects

The pattern of adverse effects seen with atropine and other antimuscarinics can mostly be related to their pharmacological actions at muscarinic and, at high doses, nicotinic receptors (see Actions of Antimuscarinics, below). These effects are dose-related and are usually reversible when therapy is stopped. The **peripheral** effects of atropine and other antimuscarinics are a consequence of their inhibitory effect on muscarinic receptors within the autonomic nervous system. At therapeutic doses, adverse effects include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations and arrhythmias, and difficulty in micturition, as well as reduction in the tone and motility of the gastrointestinal tract leading to constipation. Some of the **central** effects of atropine and other tertiary antimuscarinics seen at toxic doses (see below) may also occur at therapeutic doses.

In **overdosage**, the peripheral effects become more pronounced and other symptoms such as hyperthermia, hypertension, increased respiratory rate, and nausea and vomiting may occur. A rash may appear on the face or upper trunk. Toxic doses also cause CNS stimulation marked by restlessness, confusion, excitement, ataxia, incoordination, paranoid and psychotic reac-

tions, hallucinations and delirium, and occasionally seizures. However, in severe intoxication, central stimulation may give way to CNS depression, coma, circulatory and respiratory failure, and death.

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg for children.

Quaternary ammonium antimuscarinics, such as atropine methobromide or methonitrate and propantheline bromide, have some ganglion-blocking activity and high doses may cause orthostatic hypotension and impotence; in toxic doses non-depolarising neuromuscular block may be produced.

Systemic toxicity may be produced by the **local** instillation of antimuscarinic eye drops, particularly in children and in the elderly. Prolonged application of atropine to the eye may lead to local irritation, hyperaemia, oedema, and conjunctivitis. An increase in intra-ocular pressure may occur, especially in patients with angle-closure glaucoma.

Hypersensitivity to atropine is not uncommon and may occur as conjunctivitis or a skin rash.

Effects on body temperature. Atropine can cause hyperthermia as a result of inhibition of sweating. This may be attenuated by atropine's ability to dilate cutaneous blood vessels. However, there has been a report of hypothermia in a 14-year-old feverish patient after intravenous use of atropine.[1]

For reports of fatal heat stroke in patients taking an antimuscarinic with an antipsychotic see under Interactions in Benzatropine, p.797.

1. Lacouture PG, *et al.* Acute hypothermia associated with atropine. *Am J Dis Child* 1983; **137:** 291–2.

Effects on the eyes. In addition to the expected ocular effects of atropine (see above) there have been instances of acute angle-closure glaucoma in patients receiving nebulised atropine.[1]

1. Berdy GJ, *et al.* Angle closure glaucoma precipitated by aerosolized atropine. *Arch Intern Med* 1991; **151:** 1658–60.

Effects on the gastrointestinal tract. Antimuscarinics reduce gastrointestinal tone and paralytic ileus has been reported[1] in a 77-year-old man with Parkinson's disease who had been receiving atropine sulfate orally to control excess salivation. An increased risk of oesophageal cancer has also been reported[2] with antimuscarinics, possibly due to reductions in lower oesophageal sphincter tone increasing the risk of gastro-oesophageal reflux.

1. Beatson N. Atropine and paralytic ileus. *Postgrad Med J* 1982; **58:** 451–3.
2. Lagergren J, *et al.* Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000; **133:** 165–75.

Effects on the heart. Atropine sulfate, to a total of 1 mg per 70 kg body-weight, given intravenously to 79 patients before surgery produced arrhythmias in over 20% of patients, especially in the young.[1] Atrioventricular dissociation was the most common disturbance in adults and in children atrial rhythm disturbances were common. In another study[2] premedication including atropine or glycopyrronium given intramuscularly resulted in a significantly greater incidence of tachycardia during anaesthetic induction and intubation compared with controls who received no antimuscarinic drug. Patients who received glycopyrronium also had a higher incidence of tachycardia during surgery than the controls. No significant difference in bradycardia or extrasystoles was found in the atropine- or the glycopyrronium-treated patients. Atrial fibrillation has been reported in 2 elderly glaucoma patients after post-surgical application of atropine ointment or eye drops to the eye.[3]

1. Dauchot P, Gravenstein JS. Effects of atropine on the electrocardiogram in different age groups. *Clin Pharmacol Ther* 1971; **12:** 274–80.
2. Shipton EA, Roelofse JA. Effects on cardiac rhythm of premedication with atropine or glycopyrrolate. *S Afr Med J* 1984; **66:** 287–8.
3. Merli GJ, *et al.* Cardiac dysrhythmias associated with ophthalmic atropine. *Arch Intern Med* 1986; **146:** 45–7.

Effects on mental function. A study[1] in patients with Parkinson's disease and healthy control subjects suggested that although short-term memory was impaired in patients receiving long-term antimuscarinic therapy the effect was reversible on stopping. An epidemiological study[2] similarly reported lower cognitive performance in elderly patients receiving antimuscarinics.

See also under Trihexyphenidyl (p.820) and under Oxybutynin (p.2191).

1. Van Herwaarden G, *et al.* Short-term memory in Parkinson's disease after withdrawal of long-term anticholinergic therapy. *Clin Neuropharmacol* 1993; **16:** 438–43.
2. Lechevallier-Michel N, *et al.* Drugs with anticholinergic properties and cognitive performance in the elderly: results from the PAQUID Study. *Br J Clin Pharmacol* 2005; **59:** 143–51.

Hypersensitivity. A report[1] of anaphylactic shock developing in a 38-year-old woman after an intravenous injection of atropine.

1. Aguilera L, *et al.* Anaphylactic reaction after atropine. *Anaesthesia* 1988; **43:** 955–7.

Overdosage. Reports of atropine poisoning or overdosage have included a respiratory therapist[1] who had given 10 atropine sulfate aerosol treatments in the preceding 24 hours and children who had taken overdoses of a preparation containing diphenoxylate and atropine.[2]

1. Larkin GL. Occupational atropine poisoning via aerosol. *Lancet* 1991; **337:** 917.
2. McCarron MM, *et al.* Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature). *Pediatrics* 1991; **87:** 694–700.

Treatment of Adverse Effects

If a patient presents within an hour of an overdose of atropine by mouth the stomach may be emptied or activated charcoal given to reduce absorption. Supportive therapy should be given as required.

Physostigmine has been tried for antimuscarinic poisoning (see p.1884) but such use can be hazardous and is not generally recommended. Diazepam may be given to control marked excitement and convulsions; phenothiazines should not be given as they may exacerbate antimuscarinic effects. Antiarrhythmics are not recommended if arrhythmias develop; hypoxia and acidosis should be corrected and sodium bicarbonate may be given even if acidosis is not present.

Precautions

Atropine should be used with caution in children and the elderly, who may be more susceptible to its adverse effects. It is contra-indicated in patients with prostatic enlargement, in whom it may lead to urinary retention, and in those with paralytic ileus or pyloric stenosis. In patients with ulcerative colitis its use may lead to ileus or megacolon, and its effects on the lower oesophageal sphincter may exacerbate reflux. Caution is generally advisable in any patient with diarrhoea. It should not be given to patients with myasthenia gravis except to reduce adverse muscarinic effects of an anticholinesterase.

Atropine should not be given to patients with angle-closure glaucoma or with a narrow angle between the iris and the cornea, since it may raise intra-ocular pressure and precipitate an acute attack. Acute angle-closure glaucoma has been reported in patients receiving nebulised atropine. Some licensed product information recommends that atropine eye drops should not be used in infants aged less than 3 months due to the possible association between the induced cycloplegia and the development of amblyopia. Systemic reactions have followed the absorption of atropine from eye drops; overdosage is less likely if the eye ointment is used. In the event of blurred vision after topical application of atropine to the eye patients should not drive or operate machinery. Systemic use of antimuscarinics may also cause blurred vision, dizziness, and other effects that may impair a patient's ability to perform skilled tasks such as driving.

Because of the risk of provoking hyperthermia, atropine should not be given to patients, especially children, when the ambient temperature is high. It should also be used cautiously in patients with fever.

Atropine and other antimuscarinics need to be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, heart failure, and in cardiac surgery, where they may further accelerate the heart rate. Care is required in patients with acute myocardial infarction, as ischaemia and infarction may be made worse, and in patients with hypertension.

Atropine may cause confusion, especially in the elderly. Reduced bronchial secretion caused by systemic atropine may be associated with the formation of mucous plugs.

In the treatment of parkinsonism, increases in dosage and transfer to other forms of treatment should be gradual and the antimuscarinic should not be withdrawn abruptly. Minor reactions may be controlled by reducing the dose until tolerance has developed.

Persons with Down's syndrome appear to have an increased susceptibility to some of the actions of atropine, whereas those with albinism may have a reduced susceptibility.

Breast feeding. No adverse effects have been observed in breast-feeding infants whose mothers were receiving atropine, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)

Interactions

The effects of atropine and other antimuscarinics may be enhanced by use with other drugs having antimuscarinic properties, such as amantadine, some antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Inhibition of drug-metabolising enzymes by MAOIs may possibly enhance the effects of antimuscarinics. The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs. Antimuscarinics may also antagonise the gastrointestinal effects of cisapride, domperidone, and metoclopramide. Antimuscarinics and parasympathomimetics may counteract each others effects.

Pharmacokinetics

Atropine is readily absorbed from the gastrointestinal tract; it is also absorbed from mucous membranes, the eye, and to some extent through intact skin. It is rapidly cleared from the blood and is distributed throughout the body. It crosses the blood-brain barrier. It is incompletely metabolised in the liver and is excreted in the urine as unchanged drug and metabolites. A half-life of about 4 hours has been reported. Atropine crosses the placenta and traces appear in breast milk.

Quaternary ammonium salts of atropine, such as the methonitrate, are less readily absorbed after oral doses. They are highly ionised in body fluids and being poorly soluble in lipids they do not readily cross the blood-brain barrier.

Pregnancy. Studies of the pharmacokinetics of atropine in mother and fetus in late pregnancy[1-3] indicated that atropine rapidly crosses the placenta. However, whereas peak concentrations of atropine in fetal cord blood were reached about 5 minutes after intravenous doses, the maximum effect on fetal heart rate occurred after about 25 minutes.

1. Barrier G, *et al.* La pharmacocinétique de l'atropine chez la femme enceinte et le foetus en fin de grossesse. *Anesth Analg Reanim* 1976; **33:** 795–800.
2. Onnen I, *et al.* Placental transfer of atropine at the end of pregnancy. *Eur J Clin Pharmacol* 1979; **15:** 443–6.
3. Kanto J, *et al.* Placental transfer and pharmacokinetics of atropine after a single maternal intravenous and intramuscular administration. *Acta Anaesthesiol Scand* 1981; **25:** 85–8.

Uses and Administration

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions (see below). It is usually given as the sulfate. It first stimulates and then depresses the CNS and has antispasmodic actions on smooth muscle and reduces secretions, especially salivary and bronchial secretions; it also reduces perspiration, but has little effect on biliary or pancreatic secretion. Atropine depresses the vagus and thereby increases the heart rate. When given orally atropine reduces smooth-muscle tone and diminishes gastric and intestinal motility but has little effect on gastric secretion in usual therapeutic doses. Quaternary ammonium derivatives, such as the methonitrate, have less effect on the CNS but strong ganglion-blocking activity.

Because of its effects on heart rate, atropine is used in the treatment of bradycardia and asystole of various causes, including in acute cardiopulmonary resuscitation procedures. It has also had many other uses, including: in anaesthetic practice as a premedicant and to counteract the muscarinic effects of anticholinesterases such as neostigmine and other parasympathomimetics; as an antispasmodic in gastrointestinal disorders; as an

adjunct to opioid analgesics for the symptomatic relief of biliary or renal colic; to treat or prevent bronchospasm; and in the treatment of poisoning with mushrooms that contain muscarine and in organophosphorus pesticide poisoning. Atropine is used topically as a mydriatic and cycloplegic in ophthalmology.

See under headings below for details of dosage and administration of atropine and its derivatives in specific indications.

Actions of antimuscarinics. Antimuscarinic drugs such as atropine are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves; they are also inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation. They have been described as parasympatholytic, atropinic, atropine-like, and as anticholinergic, although the latter term should encompass compounds that also have antinicotinic actions.

At least 5 different pharmacologically identifiable types of **muscarinic receptor** (M_1, M_2, M_3, M_4, and M_5) have been described as have 5 different molecular forms (m_1, m_2, m_3, m_4, and m_5) of these receptors. While the traditional antimuscarinics appear to be relatively non-specific, newer compounds like pirenzepine and telenzepine have a selective action on the M_1 receptors within ganglia supplying cholinergic postganglionic nerves to the gastrointestinal tract.

Antimuscarinics can be classified as **tertiary amine** or **quaternary ammonium** compounds. Atropine and other naturally occurring alkaloids such as hyoscine and hyoscyamine are tertiary amines, that is they have a tertiary nitrogen atom; semisynthetic derivatives or synthetic antimuscarinics may be either tertiary (e.g. homatropine or trihexyphenidyl) or quaternary ammonium (e.g. homatropine methylbromide or ipratropium) compounds.

At therapeutic doses tertiary amine antimuscarinics have little effect on the actions of acetylcholine at nicotinic receptors. However, the quaternary ammonium antimuscarinics exhibit a greater degree of antinicotinic potency, and some of their effects at high doses are due to ganglionic blockade; excessively high doses may even produce neuromuscular block. There are also pharmacokinetic differences between tertiary amine and quaternary ammonium antimuscarinics. Quaternary ammonium compounds are less lipid soluble than tertiary amines; their gastrointestinal absorption is poor and they do not readily pass the blood-brain barrier or conjunctiva.

Antimuscarinics can produce a wide range of effects at therapeutic doses. The **peripheral** antimuscarinic effects that are produced as the dose increases are:

- decreased production of secretions from the salivary, bronchial, and sweat glands
- dilatation of the pupils (mydriasis) and paralysis of accommodation (cycloplegia)
- increased heart rate
- inhibition of micturition and reduction in gastrointestinal tone
- inhibition of gastric acid secretion

As for **central** effects, with the exception of hyoscine, which causes CNS depression at therapeutic doses, tertiary amines stimulate the medulla and higher cerebral centres producing mild central vagal excitation and respiratory stimulation. At toxic doses all tertiary amines, including hyoscine, cause stimulation of the CNS with restlessness, disorientation, hallucinations, and delirium. As the dose increases stimulation is followed by central depression and death from respiratory paralysis. Synthetic tertiary amines are less potent in their central effects than natural tertiary amines; quaternary ammonium compounds have negligible central effects.

Anaesthesia. Antimuscarinics, including *atropine*, *hyoscine*, and *glycopyrronium*, have been used pre-operatively to inhibit salivation and excessive secretions of the respiratory tract during anaesthesia (p.1780), although this use is less important now that less irritating anaesthetics are used. Atropine and glycopyrronium are also given to reduce intra-operative bradycardia and hypotension induced by drugs such as suxamethonium, halothane, or propofol, or following vagal stimulation. Glycopyrronium causes less tachycardia than atropine when given intravenously. When hyoscine is used as a premedicant it also provides some amnesia, sedation, and antiemesis but, unlike atropine, may cause bradycardia rather than tachycardia. Atropine or, preferably, glycopyrronium is also used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects (see Uses and Administration of Neostigmine, p.632).

For **premedication** 300 to 600 micrograms of atropine sulfate may be given by subcutaneous or intramuscular injection, usually 30 to 60 minutes before anaesthesia. Alternatively 300 to 600 micrograms of atropine sulfate may be given intravenously immediately before induction of anaesthesia. Suitable paediatric subcutaneous or intramuscular premedication doses of atropine sulfate are:

- children up to 3 kg in weight: 100 micrograms
- children 7 to 9 kg in weight: 200 micrograms
- children 12 to 16 kg in weight: 300 micrograms
- children over 20 kg in weight: the adult dose.

For intra-operative **bradycardia** the *BNF* states that 300 to 600 micrograms may be given intravenously; larger doses may be used in emergencies. Children may be given 10 to 20 micrograms/kg.

To counteract the muscarinic effects of **anticholinesterases** when they are used to reverse the effects of competitive muscle relaxants adults are given atropine sulfate 0.6 to 1.2 mg by intravenous injection before or with the anticholinesterase. Neonates, infants, and children may be given a dose of 20 micrograms/kg (maximum dose 600 micrograms).

Anoxic seizures. A reflex anoxic seizure is a paroxysmal event triggered by a noxious stimulus which, by vagal stimulation, causes pronounced bradycardia or cardiac arrest and consequent relative cerebral ischaemia.[1] Certain features of the attack may lead to a misdiagnosis of epilepsy. To avoid confusion with epileptic seizures (p.465), reflex anoxic seizures have also been called white or type 2 breath holding attacks. Depending on the degree of vagal hypersensitivity or noxious stimulus, attacks may occur infrequently or several times a day.

Infants and young children are mainly affected, however, the condition usually resolves by early childhood. It is generally benign and children do not suffer cardiac or cerebral damage. Treatment is seldom necessary, but atropine has been advocated to prevent vagal hypersensitivity in those children with frequent, persistent attacks. As atropine may require frequent doses with an attendant risk of overdosage, transdermal hyoscine has been tried as an alternative.[2]

1. Appleton RE. Reflex anoxic seizures. *BMJ* 1993; **307:** 214–5.
2. Palm L, Blennow G. Transdermal anticholinergic treatment of reflex anoxic seizures. *Acta Paediatr Scand* 1985; **74:** 803–4.

Biliary and renal colic. Atropine has been used as an adjunct to opioid analgesics for symptomatic relief of biliary or renal colic (see p.5).

Cardiac disorders. Atropine depresses the vagus and thereby increases the heart rate. It is therefore used in a variety of disorders or circumstances in which bradyarrhythmias occur. It is frequently used in sudden onset bradyarrhythmias and although it may also be given for the initial treatment of chronic arrhythmias (p.1160), cardiac pacing is generally preferred for long-term control. Examples of acute use include the prevention and treatment of arrhythmias associated with anaesthesia (see above), the treatment of other drug-induced arrhythmias, and in cardiac arrest due to asystole or electromechanical dissociation (pulseless electrical activity—p.1156). Atropine sulfate has been used in the management of bradycardia of acute myocardial infarction; however, caution is required, as atropine may exacerbate ischaemia or infarction in these patients.

For **advanced life support** in adults with asystole or electromechanical dissociation, European[1] and UK guidelines[2] recommend atropine in a single dose of 3 mg intravenously; US guidelines[3] recommend repeated doses of 1 mg to a total maximum dose of 3 mg.

In **bradycardia**, atropine is given[1-3] in doses of 500 micrograms intravenously repeated every 3 to 5 minutes to a total dose of 3 mg.

If an intravenous line cannot be established, atropine can be given via an endotracheal tube; 2 to 3 times the intravenous dose should be given, diluted in 10 mL of sterile water or sodium chloride 0.9%.

1. European Resuscitation Council. European Resuscitation Council guidelines for resuscitation 2005. *Resuscitation* 2005; **67** (suppl 1): S1–S190. Also available at: http://www.erc.edu/index.php/guidelines_download_2005/en/? (accessed 07/03/06)
2. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 07/03/06)
3. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112** (suppl 1): IV1–IV203. Also available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 09/02/06)

Eye disorders. Atropine is used to produce mydriasis and cycloplegia (p.1874) for ophthalmic examination. One local application can take up to 40 minutes or more to produce mydriasis, which lasts for a week or more; marked paralysis of accommodation is obtained in 1 to 3 hours with recovery in 6 to 12 days. However, other antimuscarinics such as cyclopentolate, homatropine, or tropicamide may be preferred because they have a more rapid onset and shorter duration of action than atropine. Atropine is also used in the management of uveitis and iritis, and in strabismus. It is used in the treatment of iritis and uveitis to immobilise the ciliary muscle and iris and to prevent or break down adhesions. Because of its powerful cycloplegic action atropine is also used in the determination of refraction in children below the age of 6 and in children with convergent strabismus (p.1874).

In the treatment of **inflammatory eye disorders** such as uveitis or iritis (p.1515), the dose of atropine sulfate for adults is 1 or 2 drops of a 0.5 or 1% solution instilled into the eye(s) up to four times daily. The dose in children is 1 or 2 drops of a 0.5% solution (or one drop of a 1% solution) instilled up to three times daily. For **refraction** in adults the dose is one drop of a 1% solution of atropine sulfate; this may be instilled either twice daily for 1 or 2 days before the procedure or on a single occasion one hour before the procedure. In children the dose for refraction is 1 or 2 drops of a 0.5% solution (or one drop of a 1% solution) instilled twice daily for 1 to 3 days before the procedure, with a further dose given one hour before the procedure. An ophthalmic ointment of atropine sulfate 1% may be preferred for children under 5 years and particularly in infants under 3 months who are at increased risk of systemic effects with eye drops. Some manufacturers recommend that atropine sulfate should not be used in the eyes of children younger than 3 months due to a possible association between the cycloplegia produced and the development of amblyopia.

Atropine borate has also been used in ophthalmic preparations.

References.

1. Stolovitch C, *et al.* Atropine cycloplegia: how many instillations does one need? *J Pediatr Ophthalmol Strabismus* 1992; **29:** 175–6.
2. Foley-Nolan A, *et al.* Atropine penalisation versus occlusion as the primary treatment for amblyopia. *Br J Ophthalmol* 1997; **81:** 54–7.
3. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002; **120:** 268–78.

Gastrointestinal disorders. Antimuscarinics may be used in gastrointestinal disorders as antispasmodics (see p.1692), because of their marked inhibitory effect on gastrointestinal motility, and for their antisecretory effects. Atropine (as the sulfate or quaternary derivatives such as the methobromide or methonitrate) has been used to reduce smooth-muscle tone and diminish motility, but has little effect on gastric secretion at usual therapeutic doses (about 200 micrograms of atropine sulfate). It has been tried as an adjunct to the treatment of benign gastric and duodenal ulcers and the antispasmodic action of atropine has been used to facilitate radiological examination of the gut. Atropine sulfate has also been used in the treatment of irritable bowel syndrome. Atropine oxide hydrochloride is also used for gastrointestinal disorders.

Poisoning. Atropine is used in the management of overdosage or poisoning due to anticholinesterase compounds including organophosphorus pesticides,[1,2] chemical warfare nerve gases,[3] and parasympathomimetics such as neostigmine. It is also used to antagonise the effects of cholinomimetic substances in the treatment of overdosage with parasympathomimetics such as bethanechol, and in the treatment of poisoning with mushrooms that contain muscarine. Atropine blocks the action of these compounds at muscarinic receptors, reversing bradycardia and decreasing tracheobronchial secretions, bronchoconstriction, intestinal secretions, and intestinal motility.

- In the treatment of poisoning with organophosphorus **pesticides** or chemical warfare **nerve gases** atropine sulfate may be given to adults in an initial dose of 2 mg intramuscularly or intravenously every 10 to 30 minutes until muscarinic effects disappear or signs of atropine toxicity are seen. In severe cases injections have been given as often as every 5 minutes in some centres. Continuous infusion has also been used.[4,5] A dose of at least 50 micrograms/kg has been suggested for children by some;[6] the *BNF* includes a dose of 20 micrograms/kg given every 5 to 10 minutes.
- In moderate to severe poisoning a state of atropinisation is usually maintained for at least 2 days and continued for as long as symptoms are evident. In severely poisoned patients this may entail prolonged treatment.[7,8] As large amounts of atropine may be required it is important to use a preservative-free preparation to avoid the potential toxicity associated with use of excess quantities of preservatives such as benzyl alcohol or chlorobutanol.
- Since atropine is ineffective against any nicotinic effects of these compounds a cholinesterase reactivator such as pralidoxime (p.1460) may be used as an adjunct.

The use of atropine in poisoning or overdosage with **other compounds** having muscarinic actions is similar to that for organophosphorus pesticides but the duration of treatment necessary is usually shorter. An initial dose of 0.6 to 1 mg given subcutaneously, intramuscularly, or intravenously and repeated every 2 hours may be adequate for overdosage with cholinomimetics such as bethanechol.

1. Singh S, *et al.* Is atropine alone sufficient in acute severe organophosphorus poisoning: experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995; **33:** 628–30.
2. Eddleston M, *et al.* Management of severe organophosphorus pesticide poisoning. *Crit Care* 2002; **6:** 259.
3. Anonymous. Treatment of nerve gas poisoning. *Med Lett Drugs Ther* 1995; **37:** 43–4.
4. Ram JS, *et al.* Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India* 1991; **39:** 190–3.
5. Sungur M, Güven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001; **5:** 211–15.
6. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics* 2003; **112:** 648–58.
7. Golsousidis H, Kokkas V. Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; **4:** 339–40.
8. Afzaal S, *et al.* High dose atropine in organophosphorus poisoning. *Postgrad Med J* 1990; **66:** 70–1.

Respiratory-tract disorders. Although atropine is a potent bronchodilator its use in the management of reversible airways obstruction has largely been replaced by other antimuscarinics such as ipratropium (p.1124). Atropine is sometimes used in

combination preparations with antihistamines and decongestants for the symptomatic relief of symptoms of the common cold.

References.

1. Sur S, *et al.* A random double-blind trial of the combination of nebulized atropine methylnitrate and albuterol in nocturnal asthma. *Ann Allergy* 1990; **65:** 384–8.
2. Vichyanond P, *et al.* Efficacy of atropine methylnitrate alone and in combination with albuterol in children with asthma. *Chest* 1990; **98:** 637–42.

Preparations

BP 2008: Atropine Eye Drops; Atropine Eye Ointment; Atropine Injection; Atropine Tablets; Morphine and Atropine Injection;
USP 31: Atropine Sulfate Injection; Atropine Sulfate Ophthalmic Ointment; Atropine Sulfate Ophthalmic Solution; Atropine Sulfate Tablets; Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Endotropina; Klonatropina; ***Austral.:*** Atropt; ***Belg.:*** Stellatropine; ***Braz.:*** Atropion; Sulfatina†; ***Canad.:*** Atropisol†; ***Fin.:*** Oftan Atropin†; ***Ger.:*** Atropinol†; Dysurgal; ***India:*** Bell Pino-Atrin; ***Indon.:*** Isotic Cycloma; ***Israel:*** Atrospan; ***Malaysia:*** Atrop†; ***Mex.:*** Atro Grin†; Atro Ofteno; Atropisa; Tropyn; ***NZ:*** Atropt; ***Port.:*** Atropocil; ***Switz.:*** Bellafit N; Skiatropine†; ***Turk.:*** Atrosol; ***USA:*** AtroPen; Ocu-Tropine; Sal-Tropine; ***Venez.:*** Atropicel†.

Multi-ingredient: ***Arg.:*** Asmopul†; Otorinazol†; Saldeva†; Trixol†; Yanal; ***Austral.:*** Donnagel; Donnalix; Donnatab; Neo-Diophen†; ***Austria:*** Causat; Ichtho-Bellol; Lactolavol; Myocardon; ***Braz.:*** Espasmocron; Neogrein; Ormigrein; Sedabel†; Tonaton; Vagostesyl; ***Chile:*** Buton; Dipatropin; Dispasmol†; Dolospam; Papatropin†; ***Cz.:*** Spasmoveralgin Neo†; ***Ger.:*** Ichtho-Bellol compositum S†; Ichtho-Bellol†; Mydrial-Atropin†; ***Hong Kong:*** Virulex Forte; ***Hung.:*** Meristin†; ***India:*** Atrisolon; Brovon; Pino-Cort; ***Indon.:*** Aludonna; ***Israel:*** Patropin; Spasmalgin; ***Ital.:*** Cardiostenol; Deltamidrina; Genatrop; ***Mex.:*** Paliatil; Redotex; Redotex NF; ***Pol.:*** Tolargin; ***Port.:*** Cosmaxil†; ***S.Afr.:*** Colstat; Donnatal; Famucaps; Millerspas; Virobis†; ***Spain:*** Abdominol; Midriati; Sulmetin Papaver; Sulmetin Papaverina†; Tabletas Quimpe; ***Swed.:*** Dilaudid-Atropin; ***Switz.:*** Dilaudid-Atropin†; Dolopyrine†; Nardyl; Spasmosol; ***Thai.:*** Alkamine; Alumag; Alupep; Donnatal†; Droximag†; Stomac; ***UK:*** Actonorm; Brovon; Nerve Agent Antidote L4A1; Valonorm; ***USA:*** Accuhist LA†; Alkabel; Antispasmodic Elixir; Atrosept; Barbidonna†; Bellahist-D; Bellatal; Dolsed†; Donnatal; DuoDote; Emergent-Ez; Hyosophen; MHP-A; Prosed/DS; Stahist; Susano; Trac Tabs 2X†; UAA; Uridon Modified†; Urised; Uriseptic; Uritact; ***Venez.:*** Butropina; Carbargal con Atropina; Eumidral; Fenopol†.

Used as an adjunct in: ***Austral.:*** Lofenoxal; Lomotil; ***Braz.:*** Colestase; Lomotil; ***Canad.:*** Lomotil; ***Cz.:*** Reasec; ***Fr.:*** Diarsed; ***Hong Kong:*** Dhamotil; Dimotil; Lomotil; ***Hung.:*** Reasec; ***India:*** Lomofen; Lomotil; ***Irl.:*** Lomotil; ***Malaysia:*** Atrotil†; Beamotil; Dhamotil; Lomotil†; Setmotil†; ***NZ:*** Diastop; Lomotil†; ***Pol.:*** Reasec; ***Port.:*** Lomotil†; ***S.Afr.:*** Lomotil; ***Singapore:*** Beamotil; Dhamotil; Lomotil; Remodil†; ***Thai.:*** Dilomil†; Lomotil; ***Turk.:*** Lomotil; ***UAE:*** Intard; ***UK:*** Dymotil; Lomotil; ***USA:*** Enlon-Plus†; Logen; Lomotil; Lonox; Motofen; Neostigmine Min-I-Mix; ***Venez.:*** Lomotil†.

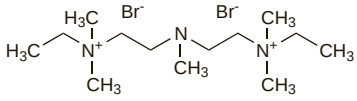
Azamethonium Bromide *(BAN, rINN)*

Azamethonii Bromidum; Azaméthonium, Bromure d'; Bromuro de azametonio; Pentamethazene Bromide; Pentaminum. 2,2′-Methyliminobis(diethyldimethylammonium) dibromide.

Азаметония Бромид

$C_{13}H_{33}Br_2N_3$ = 391.2.

CAS — 60-30-0 (azamethonium); 306-53-6 (azamethonium bromide).



Profile

Azamethonium bromide is a ganglion blocker used in the treatment of hypertension.

Azapetine Phosphate *(BANM)*

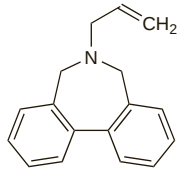
Atsapetiinifosfaatti; Azapethine Phosphate; Azapetinfosfat; Azepine Phosphate; Ro-2-3248. 6-Allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine dihydrogen phosphate.

$C_{17}H_{17}N,H_3PO_4$ = 333.3.

CAS — 146-36-1 (azapetine); 130-83-6 (azapetine phosphate).

ATC — C04AX30.

ATC Vet — QC04AX30.



(azapetine)

Profile

Azapetine is a vasodilator that has been used, as the phosphate, in peripheral vascular disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Peridil.

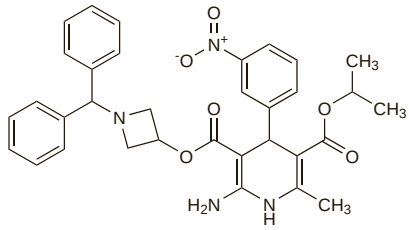
Azelnidipine *(rINN)*

Azelnidipino; Azelnidipinum; CS-905. 3-[1-(Diphenylmethyl)-3-azetidinyl] 5-isopropyl (±)-2-amino-1,4-dihydro-6-methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

Азелнидипин

$C_{33}H_{34}N_4O_6$ = 582.6.

CAS — 123524-52-7.



Profile

Azelnidipine is a long-acting dihydropyridine calcium-channel blocker used in the management of hypertension.

◊ Reviews.

1. Wellington K, Scott LJ. Azelnidipine. *Drugs* 2003; **63:** 2613–21.

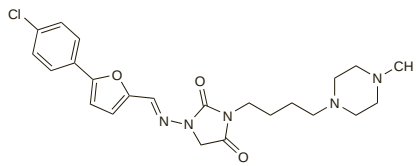
Azimilide Hydrochloride *(BANM, rINNM)*

Azimilide, Chlorhydrate d'; Azimilide Dihydrochloride *(USAN)*; Azimilidi Hydrochloridum; Hidrocloruro de azimilida; NE-10064. 1-{[5-(*p*-Chlorophenyl)furfurylidene]amino}-3-[4-(4-methyl-1-piperazinyl)butyl]hydantoin dihydrochloride.

Азимилида Гидрохлорид

$C_{23}H_{28}ClN_5O_3,2HCl$ = 530.9.

CAS — 149908-53-2 (azimilide); 149888-94-8 (azimilide hydrochloride).



(azimilide)

Profile

Azimilide hydrochloride is a class III antiarrhythmic (p.1153) being studied in the management of supraventricular arrhythmias. It has also been tried in ventricular arrhythmias.

◊ References.

1. Clemett D, Markham A. Azimilide. *Drugs* 2000; **59:** 271–7.
2. Pritchett ELC, *et al.* Effects of azimilide on heart rate and ECG conduction intervals during sinus rhythm in patients with a history of atrial fibrillation. *J Clin Pharmacol* 2002; **42:** 388–94.
3. Connolly SJ, *et al.* Symptoms at the time of arrhythmia recurrence in patients receiving azimilide for control of atrial fibrillation or flutter: results from randomized trials. *Am Heart J* 2003; **146:** 489–93.
4. Singer I, *et al.* Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004; **43:** 39–43.
5. Camm AJ, *et al.* Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004; **109:** 990–6.
6. Dorian P, *et al.* Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004; **110:** 3646–54.
7. Pritchett ELC, *et al.* Antiarrhythmic efficacy of azimilide in patients with atrial fibrillation: maintenance of sinus rhythm after conversion to sinus rhythm. *Am Heart J* 2006; **151:** 1043–9.
8. Kerr CR, *et al.* Efficacy of azimilide for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation in the presence and absence of structural heart disease. *Am J Cardiol* 2006; **98:** 215–18.
9. Pratt CM, *et al.* Cumulative experience of azimilide-associated torsades de pointes ventricular tachycardia in the 19 clinical studies comprising the azimilide database. *J Am Coll Cardiol* 2006; **48:** 471–7.
10. Lombardi F, *et al.* Azimilide vs. placebo and sotalol for persistent atrial fibrillation: the A-COMET-II (Azimilide-CardiOversion MaintEnance Trial-II) trial. *Eur Heart J* 2006; **27:** 2224–31.

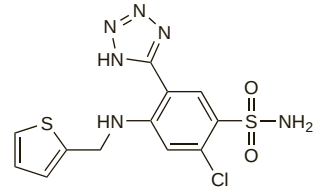
Azosemide *(USAN, rINN)* ⊗

Azosemida; Azosémide; Azosemidum; BM-02001; Ple-1053. 2-Chloro-5-(1*H*-tetrazol-5-yl)-4-(2-thenylamino)benzenesulphonamide.

Азосемид

$C_{12}H_{11}ClN_6O_2S_2$ = 370.8.

CAS — 27589-33-9.



Profile

Azosemide is a diuretic with actions similar to those of furosemide (p.1292) that has been used in the management of oedema.

Bamethan Sulfate *(USAN, rINNM)*

Bametanu siarczan; Baméthan, Sulfate de; Bamethan Sulphate *(BANM)*; Bamethani Sulfas; Sulfato de bametán. 2-Butylamino-1-(4-hydroxyphenyl)ethanol sulfate.

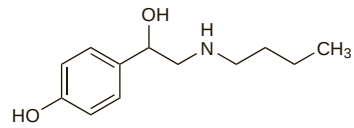
Баметана Сульфат

$(C_{12}H_{19}NO_2)_2,H_2SO_4$ = 516.6.

CAS — 3703-79-5 (bamethan); 5716-20-1 (bamethan sulfate).

ATC — C04AA31.

ATC Vet — QC04AA31.



(bamethan)

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Bamethan sulfate is a vasodilator used in the management of peripheral vascular disorders.

Bamethan nicotinate and bamethan succinate have been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dilartan; ***Braz.:*** Vasculat; ***Ger.:*** Emasex A†.

Multi-ingredient: ***Arg.:*** Flaval; Grafic Forte; Vefluxan†; ***Fr.:*** Escinogel†; ***Ger.:*** Emasex-N†; Medigel†.

Barnidipine Hydrochloride *(rINNM)*

Barnidipine, Chlorhydrate de; Barnidipini Hydrochloridum; Hidrocloruro de barnidipino; LY-198561; Mepirodipine Hydrochloride; YM-730; YM-09730-5. (+)-(3′*S*,4*S*)-1-Benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride.

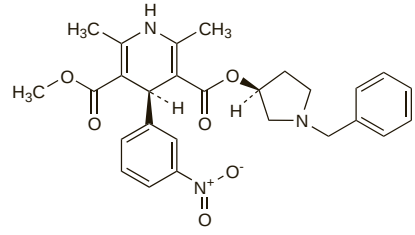
Барнидипина Гидрохлорид

$C_{27}H_{29}N_3O_6,HCl$ = 528.0.

CAS — 104713-75-9 (barnidipine); 104757-53-1 (barnidipine hydrochloride).

ATC — C08CA12.

ATC Vet — QC08CA12.



(barnidipine)