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)*

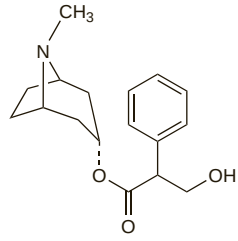
Atropiini; Atropin; Atropina; Atropinas; Atropinum; (±)-Hyoscyamine. (1*R*,3*r*,5*S*,8*r*)-Tropan-3-yl (*RS*)-tropate.

$C_{17}H_{23}NO_3$ = 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-