2. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.
3. Sabanathan K, *et al.* A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. *Eur J Clin Pharmacol* 1987; **32:** 53–60.
4. Ismail Z, *et al.* The pharmacokinetics of amiloride-hydrochlorothiazide combination in the young and elderly. *Eur J Clin Pharmacol* 1989; **37:** 167–71.

Uses and Administration

Amiloride is a weak diuretic that appears to act mainly on the distal renal tubules. It is described as potassium-sparing since, like spironolactone, it increases the excretion of sodium and reduces the excretion of potassium. Unlike spironolactone, however, it does not act by specifically antagonising aldosterone. Amiloride does not inhibit carbonic anhydrase. It takes effect about 2 hours after oral dosage and its diuretic action reaches a peak in 6 to 10 hours and has been reported to persist for about 24 hours.

Amiloride diminishes the kaliuretic effects of other diuretics, and may produce an additional natriuretic effect. It is mainly used as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the long-term treatment of oedema associated with hepatic cirrhosis (including ascites, p.1159) and heart failure (p.1165). It is also used with other diuretics in the treatment of hypertension (p.1171). Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics such as amiloride, is discussed under Effects on Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p.1308. Amiloride is sometimes used to manage hypokalaemia in primary hyperaldosteronism (p.1402).

Amiloride by inhalation has also been investigated in the management of cystic fibrosis patients with lung disease (see below).

In the treatment of **oedema** amiloride is given orally as the hydrochloride and doses are expressed in terms of the anhydrous substance. 1 mg of anhydrous hydrochloride is equivalent to about 1.14 mg of the hydrated substance. Treatment may be started with a dose of 5 to 10 mg daily, increased, if necessary, to a maximum of 20 mg daily. An initial dose of 2.5 mg once daily may be used in patients already taking other diuretics or antihypertensives. Similar doses to those given for oedema are used to reduce potassium loss in patients receiving thiazide or loop diuretics.

Potassium supplements should not be given.

Cystic fibrosis. Pulmonary disease is the major cause of mortality in cystic fibrosis (p.166). Experimental treatment aimed at modifying the pulmonary disease process has included giving amiloride by inhalation.[1,2] No evidence of pulmonary or systemic toxicity was seen in 14 patients treated for 25 weeks.[1] The mechanism of action is unclear but could be the sodium-channel blocking effect[1] or anti-inflammatory effects[3] of amiloride. Concern has been expressed[4] over possible consequences of the inhibition of endogenous urokinase by amiloride although others[5] considered this to be unlikely at the concentrations studied. However, a systematic review[6] found no evidence that amiloride was of clinical benefit.

1. Knowles MR, *et al.* A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **322:** 1189–94.
2. App EM, *et al.* Acute and long-term amiloride inhalation in cystic fibrosis lung disease: a rational approach to cystic fibrosis therapy. *Am Rev Respir Dis* 1990; **141:** 605–12.
3. Gallo RL. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 996–7.
4. Henkin J. Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997.
5. Knowles MR, *et al.* Aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **323:** 997–8.
6. Burrows E, *et al.* Sodium channel blockers for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 28/04/08).

Diabetes insipidus. Thiazide diuretics are commonly used in nephrogenic diabetes insipidus (p.2179) and NSAIDs may also be employed; both result in an overall decrease in urine production. Hydrochlorothiazide with amiloride has been reported to be at least as effective as hydrochlorothiazide plus indometacin in 5 patients.[1] In addition, amiloride obviated the need for potassium supplements. Hydrochlorothiazide with amiloride was also effective and well tolerated in a group of 4 children with nephrogenic diabetes insipidus who were treated for up to 5 years.[2]

1. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. *J Pediatr* 1990; **117:** 499–502.
2. Kirchlechner V, *et al.* Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. *Arch Dis Child* 1999; **80:** 548–52.

Renal calculi. Patients with idiopathic hypercalciuria and a history of renal calculi (p.2181) are usually given a thiazide diuretic such as hydrochlorothiazide to reduce calcium excretion. In patients with calcium oxalate calculi an inherited cellular defect in oxalate transport may also be involved and this might be corrected by amiloride.[1]

1. Baggio B, *et al.* An inheritable anomaly of red-cell oxalate transport in "primary" calcium nephrolithiasis correctable with diuretics. *N Engl J Med* 1986; **314:** 599–604.

Preparations

BP 2008: Amiloride Tablets; Co-amilofruse Tablets; Co-amilozide Oral Solution; Co-amilozide Tablets;
USP 31: Amiloride Hydrochloride and Hydrochlorothiazide Tablets; Amiloride Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Kaluril; Midamor; ***Austria:*** Midamor; ***Canad.:*** Midamor; ***Cz.:*** Amiclaran; ***Denm.:*** Amikal†; Nirulid; ***Fin.:*** Medamor†; ***Fr.:*** Modamide; ***NZ:*** Midamor; ***Swed.:*** Midamor†; ***Switz.:*** Midamor†; ***UK:*** Amilamont; ***USA:*** Midamor.

Multi-ingredient: ***Arg.:*** Amiloclor†; Diflux; Diur Pot; Diurex A; Errolon A; Furdiuren†; Hidrenox A; Lasiride; Moducren†; Moduretic; Nuriban A; Plenacor D; Prenomod†; Ren-Ur; Vericordin Compuesto; ***Austral.:*** Amizide; Moduretic; ***Austria:*** Aldoretic; Amiloral/HCT; Amiloretik; Amilorid comp; Amilostad HCT; Lanuretic; Loradur; Moducrin; Moduretic; ***Belg.:*** Belidral†; Co-Amiloride; Frusamil; Kalten†; Moduretic; ***Braz.:*** Amiretic; Diupress; Diurezin-A; Diurisa; Moduretic; ***Canad.:*** Apo-Amilzide; Gen-Amilazide; Moduret; Novamilor; Nu-Amilzide; ***Chile:*** Furdiuren; Hidrium; Hidropid; ***Cz.:*** Amicloton; Amilorid/HCT; Apo-Amilzide; Limorid†; Loradur; Moduretic; Rhefluin; ***Denm.:*** Amilco; Buram; Frusamil; Moduretic†; Sparkal; ***Fin.:*** Amitrid; Diuramin; Diurex; Miloride; Moduretic; Sparkal; ***Fr.:*** Logirene; Moducren; Moduretic; ***Ger.:*** Amilocomp beta; Amiloretik; Amilorid comp; Amilorid/HCT; Amilozid†; Aquaretic†; Diaphal; Diursan; durarese†; Esmalorid†; Moducrin; Moduretik; Tensoflux; ***Gr.:*** Frumil; Ividol; Moduretic; Tiaden; ***Hong Kong:*** Amilco†; Amithiazide; Apo-Amilzide; Moducren; Moduretic; Navispare; Sefaretic; ***Hung.:*** Amilorid Comp; Amilozid-B; ***India:*** Biduret; Frumil; Hipres-D; ***Indon.:*** Lorinid; ***Irl.:*** Amilco†; Buram; Fru-Co; Frumil; Lasoride†; Moducren; Moduret; ***Israel:*** Kaluril; ***Ital.:*** Moduretic; ***Malaysia:*** Ami-Hydrotride; Amizide; Apo-Amilzide; Moduretic; ***Mex.:*** Moduretic; ***Neth.:*** Moduretic; ***Norw.:*** Moduretic; Normorix; ***NZ:*** Amizide; Frumil; ***Pol.:*** Tialorid; ***Port.:*** Aldoretic†; Amiloride Composto†; Chibretico†; Diurene; Moducren†; Moduretic; ***S.Afr.:*** Adco-Retic; Amiloretic; Betaretic; Hexaretic; Moducren; Moduretic; Servatrin; ***Singapore:*** Apo-Amilzide; ***Spain:*** Ameride; Diuzine; Kalten; ***Swed.:*** Amiloferm; Moduretic; Normorix; Sparkal; ***Switz.:*** Agorex†; Amilo-basan†; Amiloride/HCTZ; Betadiur†; Co-Amilorid†; Comilorid; Ecodurex; Escoretic; Frumil†; Grodurex; Kalten; Moducren; Moduretic; Rhefluin; ***Thai.:*** Bilduretic; Hydrozide Plus; Hyperretic; Miduret†; Milorex†; Miretic; Modulan†; Moduretic; Moure-M; Poli-Uretic; Renase; Sefaretic; ***Turk.:*** Moduretic; ***UK:*** Amil-Co; Aridil; Burinex A; Froop Co†; Fru-Co; Frumil; Kalten; Komil; Lasoride†; Moducren†; Moduret; Moduretic; Navispare; ***USA:*** Moduretic; ***Venez.:*** Furdiuren; Moduretic.

Amiodarone *(BAN, USAN, rINN)*

Amiodaron; Amiodarona; Amiodaroni; Amiodaronum; L-3428; 51087-N; SKF-33134-A. 2-Butylbenzofuran-3-yl 4-(2-diethylaminoethoxy)-3,5-di-iodophenyl ketone.

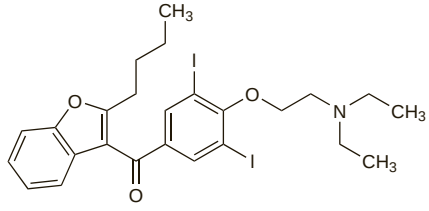
Амиодарон

$C_{25}H_{29}I_2NO_3$ = 645.3.

CAS — 1951-25-3.

ATC — C01BD01.

ATC Vet — QC01BD01.



Amiodarone Hydrochloride *(BANM, rINNM)*

Amiodaron Hidroklorür; Amiodarone, chlorhydrate d'; Amiodaron-hidroklorid; Amiodaron-hydrochlorid; Amiodaronhydroklorid; Amiodaroni hydrochloridum; Amiodaronihydrokloridi; Amjodarono hidrochloridas; Hidrocloruro de amiodarona.

Амиодарона Гидрохлорид

$C_{25}H_{29}I_2NO_3$,HCl = 681.8.

CAS — 19774-82-4.

ATC — C01BD01.

ATC Vet — QC01BD01.

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

Ph. Eur. 6.2 (Amiodarone Hydrochloride). A white or almost white, fine crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Store at a temperature not exceeding 30°. Protect from light.

Adsorption. Amiodarone is known to be adsorbed by PVC, although the amount of adsorption has varied in different studies. A study[1] using amiodarone hydrochloride 600 micrograms/mL in glucose 5% found that the concentration fell by 10% in 3 hours followed by a steady decrease to 60% of the initial concentration after 5 days when stored in flexible PVC bags at ambient temperature.[1] However, another study[2] using amiodarone hydrochloride 1.8 to 2 mg/mL in glucose 5% found only that the concentration remained 97.3% of the initial value after 24 hours in PVC infusion bags. In the first study, perfusion of the solution through PVC giving sets resulted in the concentration falling to 82% after 15 minutes, whereas the second study found the concentration fell to 95.1% after 1 hour but then returned to the initial value. No loss was noted in either study when glass or rigid PVC containers were used, suggesting that the losses were caused by the plasticiser, di-2-ethylhexylphthalate (DEHP). Amiodarone may also leach out DEHP and other plasticisers, and it has been suggested that bags and tubing containing DEHP should not be used for giving amiodarone in order to minimise patient exposure.

1. Weir SJ, *et al.* Sorption of amiodarone to polyvinyl chloride infusion bags and administration sets. *Am J Hosp Pharm* 1985; **42:** 2679–83.
2. Peters PG, Hayball PJ. A comparative analysis of the loss of amiodarone from small and large volume PVC and non-PVC infusion systems. *Anaesth Intensive Care* 1990; **18:** 241–5.

Incompatibility. Amiodarone injection has been reported to be incompatible with aminophylline,[1] flucloxacillin,[2] heparin,[3] and sodium bicarbonate.[4] A further study[5] reported incompatibility with ampicillin/sulbactam sodium, ceftazidime sodium, digoxin, furosemide, imipenem/cilastatin sodium, magnesium sulfate, piperacillin sodium, piperacillin/tazobactam sodium, potassium phosphate, and sodium phosphate. UK licensed product information states that it is incompatible with sodium chloride solutions.

1. Hasegawa GR, Eder JF. Visual compatibility of amiodarone hydrochloride injection with other injectable drugs. *Am J Hosp Pharm* 1984; **41:** 1379–80.
2. Taylor A, Lewis R. Amiodarone and injectable drug incompatibility. *Pharm J* 1992; **248:** 533.
3. Cairns CJ. Incompatibility of amiodarone. *Pharm J* 1986; **236:** 68.
4. Korth-Bradley JM. Incompatibility of amiodarone hydrochloride and sodium bicarbonate injections. *Am J Health-Syst Pharm* 1995; **52:** 2340.
5. Chalmers JR, *et al.* Visual compatibility of amiodarone hydrochloride injection with various intravenous drugs. *Am J Health-Syst Pharm* 2001; **58:** 504–6.

Stability. An oral suspension prepared from tablets[1] and containing amiodarone hydrochloride 5 mg/mL was stable for 3 months at 4° and 6 weeks at 25°.

1. Nahata MC. Stability of amiodarone in an oral suspension stored under refrigeration and at room temperature. *Ann Pharmacother* 1997; **31:** 851–2.

Adverse Effects and Treatment

Adverse effects are common with amiodarone. Many are dose-related and reversible with reduction in dose; however, because of its long half-life this can take some time and adverse effects may develop after treatment is stopped.

Adverse cardiovascular effects associated with amiodarone include severe bradycardia, sinus arrest, and conduction disturbances. Severe hypotension may follow intravenous use, particularly (though not exclusively) at rapid infusion rates. Amiodarone may also produce ventricular tachyarrhythmias; torsade de pointes has been reported but appears to be less of a problem with amiodarone than other antiarrhythmics. Rarely, heart failure may be precipitated or aggravated.

Amiodarone reduces the peripheral transformation of thyroxine (T_4) to tri-iodothyronine (T_3) and increases the formation of reverse-T_3. It can affect thyroid function and may induce hypo- or hyperthyroidism.

There have been reports of severe pulmonary toxicity including pulmonary fibrosis and interstitial pneumonitis. These effects are usually reversible on withdrawal of amiodarone but are potentially fatal.

Amiodarone can adversely affect the liver. There may be abnormal liver function tests and cirrhosis or hepatitis; fatalities have been reported.

Prolonged use of amiodarone causes the development of benign yellowish-brown corneal microdeposits in the majority of patients, sometimes associated with coloured haloes of light; these are reversible on stopping therapy. Photosensitivity reactions are also common and more rarely blue-grey discoloration of the skin may occur.

Other adverse effects reported include benign intracranial hypertension, haemolytic or aplastic anaemia, peripheral neuropathy, paraesthesias, myopathy, ataxia, tremor, nausea, vomiting, a metallic taste, nightmares, headaches, sleeplessness, fatigue, and epididymitis.

Thrombophlebitis can occur if amiodarone is injected regularly or infused for prolonged periods into a peripheral vein. Rapid intravenous injection has been associated with anaphylactic shock, hot flushes, sweating, and nausea.

It has been suggested that amiodarone-induced phospholipidosis may explain some of its adverse effects. Amiodarone's iodine content contributes to its thyrotoxicity.

◊ Reviews of the adverse effects of amiodarone.

1. Naccarelli GV, *et al.* Adverse effects of amiodarone: pathogenesis, incidence and management. *Med Toxicol Adverse Drug Exp* 1989; **4:** 246–53.
2. Kerin NZ, *et al.* Long-term efficacy and toxicity of high- and low-dose amiodarone regimens. *J Clin Pharmacol* 1989; **29:** 418–23.
3. Perkins MW, *et al.* Intraoperative complications in patients receiving amiodarone: characteristics and risk factors. *DICP Ann Pharmacother* 1989; **23:** 757–63.
4. Vrobel TR, *et al.* A general overview of amiodarone toxicity: its prevention, detection, and management. *Prog Cardiovasc Dis* 1989; **31:** 393–426.
5. Morgan DJR. Adverse reactions profile: amiodarone. *Prescribers' J* 1991; **31:** 104–11.
6. Committee on Safety of Medicines/Medicines Control Agency. Amiodarone (Cordarone X). *Current Problems* 1996; **22:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 21/06/07)
7. Vorperian VR, *et al.* Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997; **30:** 791–8.
8. Bongard V, *et al.* Incidence rate of adverse drug reactions during long-term follow-up of patients newly treated with amiodarone. *Am J Ther* 2006; **13:** 315–19.

Effects on electrolyte balance. Hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone has been reported[1-4] in patients taking amiodarone. In each case, the hyponatraemia improved when the dose was reduced or amiodarone was stopped.

1. Odeh M, *et al.* Hyponatremia during therapy with amiodarone. *Arch Intern Med* 1999; **159:** 2599–2600.
2. Ikegami H, *et al.* Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by amiodarone: a report on two cases. *J Cardiovasc Pharmacol Ther* 2002; **7:** 25–8.
3. Patel GP, Kasiar JB. Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002; **22:** 649–51.
4. Aslam MK, *et al.* Syndrome of inappropriate antidiuretic hormone secretion induced by amiodarone therapy. *Pacing Clin Electrophysiol* 2004; **27:** 831–2.

Effects on the eyes. Slit-lamp examination showed corneal abnormalities in 103 of 105 patients treated with amiodarone for 3 months to 7 years.[1] The most advanced abnormality comprised whorled patterns with uniform granular opacities. The corneal deposits became denser if amiodarone dosage was increased and regressed if dosage was reduced. Ocular symptoms were reported in only 12 patients. Photophobia was reported in 3 patients, while 2 had visual haloes, 1 had blurring of vision, and a further 6 had lid irritation. However, lid irritation was considered a photosensitive skin reaction and blurred vision was probably not due to amiodarone. No patient had any deterioration in visual acuity attributable to amiodarone. In 16 patients amiodarone was withdrawn with complete clearing of corneal abnormalities within 7 months and routine ophthalmological monitoring was considered unnecessary in patients without ocular symptoms. However, optic neuropathy[2-4] and neuritis with visual impairment have been reported with amiodarone and UK licensed product information recommends that annual ophthalmological examinations should be performed.

A sicca syndrome with diminished tear and saliva production has been reported[5] during amiodarone treatment.

1. Ingram DV, *et al.* Ocular changes resulting from therapy with amiodarone. *Br J Ophthalmol* 1982; **66:** 676–9.
2. Feiner LA, *et al.* Optic neuropathy and amiodarone therapy. *Mayo Clin Proc* 1987; **62:** 702–17.
3. Macaluso DC, *et al.* Features of amiodarone-induced optic neuropathy. *Am J Ophthalmol* 1999; **127:** 610–12.
4. Johnson LN, *et al.* The clinical spectrum of amiodarone-associated optic neuropathy. *J Natl Med Assoc* 2004; **96:** 1477–91.
5. Dickinson EJ, Wolman RL. Sicca syndrome associated with amiodarone therapy. *BMJ* 1986; **293:** 510.

Effects on the genitalia. Epididymal swelling and scrotal pain have been reported with amiodarone.[1-3] Time to onset varied from 7 to 71 months after starting treatment, and resolution occurred within 10 weeks despite continuation of amiodarone in some patients. The mechanism of the reaction is unknown, but in 1 patient[2] the concentration of desethylamiodarone in semen was fivefold that in serum.

Brown discoloration of semen and sweat has also been associated with amiodarone therapy.[4]

1. Gasparich JP, *et al.* Non-infectious epididymitis associated with amiodarone therapy. *Lancet* 1984; **ii:** 1211–12.
2. Ward MJ, *et al.* Association of seminal desethylamiodarone concentration and epididymitis with amiodarone treatment. *BMJ* 1988; **296:** 19–20.
3. Sadek I, *et al.* Amiodarone-induced epididymitis: report of a new case and literature review of 12 cases. *Can J Cardiol* 1993; **9:** 833–6.
4. Adams PC, *et al.* Amiodarone in testis and semen. *Lancet* 1985; **i:** 341.

Effects on the heart. Amiodarone has the potential to provoke arrhythmias; it prolongs the QT interval and there have been reports of torsade de pointes. However, a review of the literature[1] indicated that the frequency of proarrhythmic events was low. The risk of torsade de pointes also appears to be lower with amiodarone than with other class III antiarrhythmics, possibly due to additional actions of amiodarone such as blockade of calcium channels.[2]

1. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
2. Brendorp B, *et al.* A benefit-risk assessment of class III antiarrhythmic agents. *Drug Safety* 2002; **25:** 847–65.

Effects on lipid metabolism. Amiodarone increases phospholipid concentrations in tissues and this may be responsible for some of its adverse effects.[1] Although hyperlipidaemia may result from hypothyroidism, amiodarone can also increase serum-cholesterol concentrations independently of any effect on the thyroid.[2,3] The effect on triglyceride concentrations is not clear.[3]

1. Kodavanti UP, Mehendale HM. Cationic amphiphilic drugs and phospholipid storage disorder. *Pharmacol Rev* 1990; **42:** 327–54.
2. Wiersinga WM, *et al.* An increase in plasma cholesterol independent of thyroid function during long-term amiodarone therapy: a dose-dependent relationship. *Ann Intern Med* 1991; **114:** 128–32.
3. Lakhdar AA, *et al.* Long-term amiodarone therapy raises serum cholesterol. *Eur J Clin Pharmacol* 1991; **40:** 477–80.

Effects on the liver. Plasma concentrations of liver enzymes are often increased in patients taking amiodarone but this is usually asymptomatic. However, there have been reports of hepatic injury,[1,2] including hepatitis and cirrhosis, with histological changes resembling alcoholic liver disease.[1] Fatal cirrhosis has been reported, usually in patients receiving high doses or long-term therapy,[3-8] and may develop after stopping amiodarone. However, rapidly progressive fatal hepatic failure has occurred[9] only one month after starting treatment. There have also been reports of severe cholestasis, including a case that was reversible,[10] and another that was fatal, despite amiodarone being stopped.[11] Acute hepatitis occurring within 24 hours of intravenous amiodarone has been reported,[12-14] but in 1 case[13] did not recur with subsequent oral therapy, suggesting that the reaction may have been related to the vehicle used in the intravenous formulation.

1. Simon JB, *et al.* Amiodarone hepatotoxicity simulating alcoholic liver disease. *N Engl J Med* 1984; **311:** 167–72.
2. Babatin M, *et al.* Amiodarone hepatotoxicity. *Curr Vasc Pharmacol* 2008; **6:** 228–36.
3. Lim PK, *et al.* Neuropathy and fatal hepatitis in a patient receiving amiodarone. *BMJ* 1984; **288:** 1638–9.
4. Tordjman K, *et al.* Amiodarone and the liver. *Ann Intern Med* 1985; **102:** 411–12.
5. Rinder HM, *et al.* Amiodarone hepatotoxicity. *N Engl J Med* 1986; **314:** 318–19.
6. Richer M, Robert S. Fatal hepatotoxicity following oral administration of amiodarone. *Ann Pharmacother* 1995; **29:** 582–6.
7. Singhal A, *et al.* Low dose amiodarone causing pseudo-alcoholic cirrhosis. *Age Ageing* 2003; **32:** 224–5.
8. Oikawa H, *et al.* Liver cirrhosis induced by long-term administration of a daily low dose of amiodarone: a case report. *World J Gastroenterol* 2005; **11:** 5394–7.
9. Lwakatare JM, *et al.* Fatal fulminating liver failure possibly related to amiodarone treatment. *Br J Hosp Med* 1990; **44:** 60–1.
10. Morse RM, *et al.* Amiodarone-induced liver toxicity. *Ann Intern Med* 1988; **109:** 838–40.
11. Chang C-C, *et al.* Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Arch Pathol Lab Med* 1999; **123:** 251–6.
12. Pye M, *et al.* Acute hepatitis after parenteral amiodarone administration. *Br Heart J* 1988; **59:** 690–1.
13. James PR, Hardman SMC. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. *Heart* 1997; **77:** 583–4.
14. Chan AL, *et al.* Fatal amiodarone-induced hepatotoxicity: a case report and literature review. *Int J Clin Pharmacol Ther* 2008; **46:** 96–101.

Effects on the lungs. Pulmonary toxicity is one of the most severe adverse effects associated with amiodarone therapy. Reviews[1] have suggested that it may occur in up to 10% of patients (although the incidence in controlled studies appears to be lower[2]) and fatalities have been reported.[3,4] The onset is usually chronic, and patients often present several months after starting amiodarone with increasing dyspnoea, cough, and pleuritic chest pain; however, the onset may also be more acute, and in one patient[5] occurred within days of starting amiodarone. Acute reactions have also developed in patients undergoing surgery or other procedures;[2,6] two patients with amiodarone pulmonary toxicity died less than 1 hour and 24 hours, respectively after pulmonary angiography.[7] Different forms of toxicity have been reported, including interstitial and alveolar infiltration,[8] fibrosis,[3] and pneumonitis;[9] amiodarone-induced asthma has also been reported.[10] Although there is some evidence that toxicity is dose-related,[8] it has also occurred at low doses,[11] and different mechanisms may be involved;[1,6] some patients have evidence of direct toxicity, while in others[9] an immunological reaction appears to be involved. Most patients recover gradually if amiodarone is stopped, but treatment with corticosteroids may be given if necessary,[1,8] and has been particularly recommended[6] in acute lung injury.

1. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: recognition and pathogenesis. *Chest* 1988; **93:** 1067–75 (part 1) and 1242–8 (part 2).
2. Sunderji R, *et al.* Pulmonary effects of low dose amiodarone: a review of the risks and recommendations for surveillance. *Can J Cardiol* 2000; **16:** 1435–40.
3. Morera J, *et al.* Amiodarone and pulmonary fibrosis. *Eur J Clin Pharmacol* 1983; **24:** 591–3.
4. Committee on Safety of Medicines. Recurrent ventricular tachycardia: adverse drug reactions. *BMJ* 1986; **292:** 50.
5. Goldstein I, *et al.* Very early onset of acute amiodarone pulmonary toxicity presenting with hemoptysis. *Chest* 1997; **111:** 1446–7.
6. Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? *Chest* 2001; **120:** 275–82.
7. Wood DL, *et al.* Amiodarone pulmonary toxicity: report of two cases associated with rapidly progressive fatal adult respiratory distress syndrome after pulmonary angiography. *Mayo Clin Proc* 1985; **60:** 601–3.
8. Marchlinski FE, *et al.* Amiodarone pulmonary toxicity. *Ann Intern Med* 1982; **97:** 839–45.
9. Venet A, *et al.* Five cases of immune-mediated amiodarone pneumonitis. *Lancet* 1984; **i:** 962–3.
10. Yavuzgil O, *et al.* New-onset bronchial asthma induced by low-dose amiodarone. *Ann Pharmacother* 2005; **39:** 385–6.
11. Ott MC, *et al.* Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest* 2003; **123:** 646–51.

Effects on mental state. There have been isolated reports of patients (age range 54 to 80 years) developing delirium within about 4 to 17 days of starting amiodarone therapy.[1-3] Mental status improved on withdrawal of amiodarone.

1. Trohman RG, *et al.* Amiodarone-induced delirium. *Ann Intern Med* 1988; **108:** 68–9.
2. Barry JJ, Franklin K. Amiodarone-induced delirium. *Am J Psychiatry* 1999; **156:** 1119.
3. Athwal H, *et al.* Amiodarone-induced delirium. *Am J Geriatr Psychiatry* 2003; **11:** 696–7.

Effects on the nervous system. Neurological toxicity is a recognised adverse effect of amiodarone. A study[1] in 10 patients treated with amiodarone for more than 2 years found that 3 had evidence of peripheral neuropathy, possibly correlated with high doses and high serum concentrations of amiodarone.

1. Fraser AG, McQueen INF. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 612.

Effects on the pancreas. Pancreatitis has been reported[1] in a patient 4 days after starting amiodarone. Symptoms resolved after withdrawal of the drug but returned on re-exposure.

1. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone. *Lancet* 1997; **350:** 1300.

Effects on the skin and hair. The most common adverse skin reaction associated with amiodarone is photosensitivity. This is a phototoxic rather than a photoallergic reaction[1-3] and the wavelengths responsible extend from the long-wave ultraviolet (UVA) into the visible light range.[1] Affected patients should be advised to wear protective clothing and avoid exposure to sunlight. Topical sunblock preparations, such as those containing zinc or titanium oxides, may reduce the risk of reaction and a reduction in amiodarone dosage may also be useful.[1] Although pyridoxine has been reported[4] to protect against amiodarone-induced photosensitivity, results from a double-blind placebo-controlled study[5] indicated that it may enhance the photosensitivity. Photosensitivity may continue for several weeks after withdrawal of amiodarone due to its extensive distribution, and persistence for longer periods has been reported.[6] There have also been reports[7] of basal cell carcinoma, possibly related to amiodarone-induced photosensitivity.

Blue-grey[2,3,8] and golden-brown[3] pigmentation of light-exposed skin have been reported during long-term amiodarone use. The pigmentation is usually slowly reversible on withdrawing amiodarone but may not completely disappear. The mean concentrations of amiodarone and its desethyl metabolite in light-exposed pigmented skin have been found to be 10 times the concentrations in non-exposed skin.[2] Discoloration of semen and sweat has also been noted (see Effects on the Genitalia, above).

Cutaneous vasculitis,[9,10] exfoliative dermatitis,[11] and fatal toxic epidermal necrolysis[12,13] have been reported. Alopecia[14,15] has been associated with amiodarone but increased hair growth,[3] possibly due to the vasodilator activity of amiodarone, has also been reported. Extravasation of amiodarone injection has caused severe skin necrosis.[16]

1. Ferguson J, *et al.* Prevention of amiodarone-induced photosensitivity. *Lancet* 1984; **ii:** 414.
2. Zachary CB, *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110:** 451–6.
3. Ferguson J, *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113:** 537–49.
4. Kaufmann G. Pyridoxine against amiodarone-induced photosensitivity. *Lancet* 1984; **i:** 51–2.
5. Mulrow JP, *et al.* Pyridoxine and amiodarone-induced photosensitivity. *Ann Intern Med* 1985; **103:** 68–9.
6. Yones SS, *et al.* Persistent severe amiodarone-induced photosensitivity. *Clin Exp Dermatol* 2005; **30:** 500–502.

7. Hall MA, *et al.* Basalioma after amiodarone therapy—not only in Britain. *Br J Dermatol* 2004; **151:** 932–3.
8. Ammoury A, *et al.* Photodistribution of blue-gray hyperpigmentation after amiodarone treatment: molecular characterization of amiodarone in the skin. *Arch Dermatol* 2008; **144:** 92–6.
9. Starke ID, Barbatis C. Cutaneous vasculitis associated with amiodarone therapy. *BMJ* 1985; **291:** 940.
10. Gutierrez R, *et al.* Vasculitis associated with amiodarone treatment. *Ann Pharmacother* 1994; **28:** 537.
11. Moots RJ, Banerjee A. Exfoliative dermatitis after amiodarone treatment. *BMJ* 1988; **296:** 1332–3.
12. Bencini PL, *et al.* Toxic epidermal necrolysis and amiodarone treatment. *Arch Dermatol* 1985; **121:** 838.
13. Yung A, *et al.* Two unusual cases of toxic epidermal necrolysis. *Australas J Dermatol* 2002; **43:** 35–8.
14. Samanta A, *et al.* Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287:** 503.
15. Samuel LM, *et al.* Amiodarone and hair loss. *Postgrad Med J* 1992; **68:** 771.
16. Russell SJ, Saltissi S. Amiodarone induced skin necrosis. *Heart* 2006; **92:** 1395.

Effects on thyroid function. Amiodarone has complex effects on thyroid function[1-3] and, while the majority of euthyroid patients receiving amiodarone remain clinically euthyroid, both hypo- and hyperthyroidism may occur. Amiodarone has direct effects on the thyroid gland, but also alters serum concentrations of thyroid hormones, complicating the interpretation of thyroid function tests. Use of amiodarone results in a reduction of the peripheral conversion of thyroxine (T_4) to tri-iodothyronine (T_3) with a resulting increase in T_4, a modest fall in T_3, and an increase in reverse-T_3 concentrations; the basal serum-TSH (thyroid-stimulating hormone; thyrotrophin) concentration rises initially but tends to return to normal after about 3 months of treatment.

The prevalence of clinical hypo- and hyperthyroidism appears to correlate with dietary iodine intake, with hypothyroidism being more common in areas of adequate iodine intake and hyperthyroidism in areas of lower intake; the overall incidence of thyroid disorders has been suggested[2] to be anywhere between 1 to 32%. Although the exact mechanism for the toxicity is not known, amiodarone has a high iodine content (about 75 mg of iodine in each 200-mg tablet) and the large iodine load may affect the thyroid, particularly in patients with an underlying subclinical thyroid defect. Auto-immune mechanisms may also contribute and antithyroid antibodies have been detected during amiodarone therapy. The high iodine load appears to be the main mechanism for hypothyroidism, but for hyperthyroidism two mechanisms may be involved. Type I amiodarone-induced thyrotoxicosis appears to be precipitated by the iodine load, whereas type II amiodarone-induced thyrotoxicosis is a destructive thyroiditis that is probably caused by a direct toxic effect on the thyroid gland.

Assessment of thyroid function is recommended in patients before starting amiodarone treatment and periodically during treatment; TSH concentrations should be measured, along with free T_3 and T_4.

Amiodarone-induced hypothyroidism usually presents similarly to other forms of hypothyroidism[1-3] and treatment is with levothyroxine, starting with a low dose and gradually increasing until control is achieved; amiodarone may be continued.

Amiodarone-induced hyperthyroidism is a more complex problem and may be difficult to diagnose and manage.[1-4] Patients may present with classical symptoms such as tachycardia, tremor, weight loss, nervousness, and irritability, but in other cases reappearance of angina, or a worsening of arrhythmia may be the only indication. Amiodarone is usually stopped if clinical hyperthyroidism develops, but may be continued if necessary while the hyperthyroidism is treated.[1-5] Management depends on whether the patient has type I or type II hyperthyroidism. Treatment of type I is usually with the thiourea drugs carbimazole, thiamazole, or propylthiouracil; in resistant cases potassium perchlorate may be used with a thiourea to reduce the thyroid iodine load. Lithium carbonate has been used as an alternative, but its role is not yet established.[1,2] In type II thyrotoxicosis, treatment is usually with corticosteroids, and they may also be used with thioureas where the type is mixed or unclear. Oral cholecystographic contrast media such as iopanoic acid have also been used, but appear to be less effective.[6] Radio-iodine can be used but may not be effective if the uptake of radio-iodine by the thyroid is low due to the iodine load from amiodarone; radio-iodine has also been used[7] to allow amiodarone to be restarted in patients with a history of amiodarone-induced hyperthyroidism. Thyroidectomy may have a role[1-4,8] in the treatment of resistant amiodarone-induced hyperthyroidism.

1. Loh K-C. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000; **76:** 133–40.
2. Martino E, *et al.* The effects of amiodarone on the thyroid. *Endocr Rev* 2001; **22:** 240–54.
3. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med* 2005; **118:** 706–14.
4. Bartalena L, *et al.* Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.
5. Uzan L, *et al.* Continuation of amiodarone therapy despite type II amiodarone-induced thyrotoxicosis. *Drug Safety* 2006; **29:** 231–6.
6. Bogazzi F, *et al.* Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab* 2003; **88:** 1999–2002.
7. Hermida J-S, *et al.* Radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis. *Am J Med* 2004; **116:** 345–8.
8. Gough IR, Gough J. Surgical management of amiodarone-associated thyrotoxicosis. *Med J Aust* 2002; **176:** 128–9.

Lupus. There have been reports[1-3] of lupus developing in patients treated with amiodarone; the condition improved when amiodarone was stopped.

1. Susano R, *et al.* Amiodarone induced lupus. *Ann Rheum Dis* 1999; **58:** 655–6.
2. Sheikhzadeh A, *et al.* Drug-induced lupus erythematosus by amiodarone. *Arch Intern Med* 2002; **162:** 834–6.
3. Kundu AK. Amiodarone-induced systemic lupus erythematosus. *J Assoc Physicians India* 2003; **51:** 216–17.

Precautions

Amiodarone should not be given to patients with bradycardia, sino-atrial block, AV block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure. It may be used, but with caution, in patients with heart failure. Electrolyte disorders should be corrected before starting treatment. The use of amiodarone should be avoided in patients with iodine sensitivity, or evidence or history of thyroid disorders. Patients taking amiodarone should avoid exposure to sunlight.

Thyroid function should be monitored regularly in order to detect amiodarone-induced hyper- or hypothyroidism. Thyroxine, tri-iodothyronine, and thyrotrophin (thyroid-stimulating hormone; TSH) concentrations should be measured; clinical assessment is important but is unreliable alone. See also Effects on Thyroid Function under Adverse Effects and Treatment, above.

Tests of liver and pulmonary function should also be carried out regularly in patients on long-term therapy. Ophthalmological examinations should be performed annually. Although urinary excretion is not a major route for the elimination of amiodarone or its metabolites, there is a possibility of iodine accumulation in renal impairment.

Intravenous injections of amiodarone should be given slowly: if prolonged or repeated infusions are envisaged, the use of a central venous catheter should be considered.

Some of the contra-indications for amiodarone may not apply when it is given intravenously in emergency situations.

Administration. For the problems of controlling the delivery rate of amiodarone by intravenous infusion, see under Uses and Administration, below.

Breast feeding. Amiodarone is distributed into breast milk[1,2] and significant amounts may be ingested if infants are breast fed. Licensed product information therefore contra-indicates the use of amiodarone during breast feeding, and the American Academy of Pediatrics considers[3] that the use of amiodarone may be of concern due to the risk of hypothyroidism in the infant. In one study,[2] amiodarone was still detectable in breast milk several weeks after amiodarone was stopped, suggesting that caution is still required. However, there has been a report[4] of an infant who was successfully breast fed with close monitoring of thyroid function; the mother stopped amiodarone at delivery.

1. Pitcher D, *et al.* Amiodarone in pregnancy. *Lancet* 1983; **i:** 597–8.
2. Plomp TA, *et al.* Use of amiodarone during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; **43:** 201–7.
3. 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 10/07/07)
4. Hall CM, McCormick KPB. Amiodarone and breast feeding. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F255–F258.

Porphyria. Amiodarone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy. Each 200-mg tablet of amiodarone contains about 75 mg of iodine. The potential effect of this iodine load on the fetus has limited the use of amiodarone in pregnancy since iodine freely crosses the placenta and may cause thyroid disorders in the fetus. In addition, amiodarone and desethylamiodarone both cross the placenta, with respective concentrations in cord blood at delivery of about 10% and 25% of the maternal plasma concentrations, and direct effects on the fetus are therefore possible. However, a review[1] of 64 reported cases of amiodarone use during pregnancy found no evidence of an increased incidence of fetal malformations; hypothyroidism occurred in 14 neonates (22%), but only 2 had detectable goitre, and 2 neonates had transient hyperthyroidism. Neurodevelopmental follow-up was limited, but mild abnormalities were reported in some cases; this appeared to be independent of thyroid status, suggesting it may have been due to a direct effect of amiodarone.

1. Bartalena L, *et al.* Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001; **24:** 116–30.

Interactions

Amiodarone should be used with caution with other drugs liable to induce bradycardia, such as beta blockers or calcium-channel blockers, and with other antiarrhythmic drugs. Use with arrhythmogenic drugs, particularly drugs that prolong the QT interval such as phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided. Drugs that cause hypokalaemia or hypomagnesaemia may also increase the risk of arrhythmias with amiodarone. Amiodarone is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8 and interactions may occur with inhibitors of these enzymes, particularly with inhibitors of CYP3A4 such as HIV-protease inhibitors, cimetidine, and grapefruit juice. Enzyme inducers such as rifampicin and phenytoin may reduce amiodarone concentrations. In addition, amiodarone is an inhibitor of some cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6, resulting in higher plasma concentrations of other drugs metabolised by these enzymes. Examples of these include ciclosporin, clonazepam, digoxin, flecainide, phenytoin, procainamide, quinidine, simvastatin, and warfarin. Amiodarone also inhibits P-glycoprotein and could affect drugs that are P-glycoprotein substrates.

◊ Reviews.

1. Marcus FI. Drug interactions with amiodarone. *Am Heart J* 1983; **106:** 924–30.
2. Lesko LJ. Pharmacokinetic drug interactions with amiodarone. *Clin Pharmacokinet* 1989; **17:** 130–40.

Agalsidase. For the effect of the use of amiodarone with *agalsidase alfa* or *beta*, see p.2252.

Antibacterials. Palpitations and activation of an implantable cardioverter defibrillator occurred[1] in a woman receiving amiodarone when *rifampicin* was added. Serum concentrations of amiodarone were reduced, probably due to induction of metabolising enzymes by rifampicin.

1. Zarembski DG, *et al.* Impact of rifampin on serum amiodarone concentrations in a patient with congenital heart disease. *Pharmacotherapy* 1999; **19:** 249–51.

Antiepileptics. The interaction between *phenytoin* and amiodarone resulting in increased plasma-phenytoin concentrations is widely recognised (see p.498). However, phenytoin is a hepatic enzyme inducer and has been reported[1] to decrease serum-amiodarone concentrations by 32 and 49% after 1 and 2 weeks of use respectively.

1. Nolan PE, *et al.* Effect of phenytoin on the clinical pharmacokinetics of amiodarone. *J Clin Pharmacol* 1990; **30:** 1112–19.

Antivirals. A potential interaction has been suggested between amiodarone and HIV-protease inhibitors due to inhibition of amiodarone metabolism. Raised serum concentrations of amiodarone have been reported[1] in a patient who received *indinavir* for postexposure prophylaxis; no clinical signs of toxicity occurred.

1. Lohman JJHM, *et al.* Antiretroviral therapy increases serum concentrations of amiodarone. *Ann Pharmacother* 1999; **33:** 645–6.

Grapefruit juice. A study[1] in healthy subjects reported that grapefruit juice decreased the metabolism of amiodarone; the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration of amiodarone were both increased.

1. Libersa CC, *et al.* Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* 2000; **49:** 373–8.

Histamine H_2-antagonists. *Cimetidine* inhibits hepatic metabolism and an increase in the serum-amiodarone concentration has been reported[1] in 8 out of 12 patients given amiodarone and cimetidine.

1. Hogan C, *et al.* Cimetidine-amiodarone interaction. *J Clin Pharmacol* 1988; **28:** 909.

Theophylline. For a report of increased serum-theophylline concentrations and resultant adverse effects in a patient when amiodarone was added to therapy, see Antiarrhythmics, p.1142.

Pharmacokinetics

Amiodarone is absorbed variably and erratically from the gastrointestinal tract; the average bioavailability is about 50%, but varies widely, and both the rate and extent of absorption are increased by food. It is extensively

distributed to body tissues and accumulates notably in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen; it has been reported to be about 96% bound to plasma proteins. The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for a month or more. A major metabolite, desethylamiodarone, has antiarrhythmic properties. There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur. Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

After intravenous injection the maximum effect is achieved within 1 to 30 minutes and persists for 1 to 3 hours.

◊ Reviews.

1. Latini R, *et al.* Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet* 1984; **9:** 136–56.
2. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; **72:** 45F–50F.

Uses and Administration

Amiodarone is an antiarrhythmic with mainly class III properties (see p.1153). It is used in the control of ventricular and supraventricular arrhythmias, including arrhythmias associated with Wolff-Parkinson-White syndrome. It has been tried for the prevention of arrhythmias in patients with myocardial infarction or heart failure.

Amiodarone hydrochloride is given orally in initial doses of 200 mg three times daily for a week, then 200 mg twice daily for a week, and then a usual maintenance dosage of 200 mg or less daily, according to response. In the USA, amiodarone is only licensed for ventricular arrhythmias and higher doses are used: loading doses of amiodarone hydrochloride are up to 1.6 g daily for 1 to 3 weeks, followed by 600 to 800 mg daily for a month, then a usual maintenance dose of 400 mg daily. Consideration should be given to potential adverse effects, and patients should be given the minimum effective dose.

Amiodarone hydrochloride may be given intravenously where facilities for close monitoring of cardiac function and resuscitation are available. It is usually given as a dilute solution in glucose 5%. Solutions containing less than 600 micrograms/mL are unstable but high concentrations are irritating to the veins, and solutions containing more than 2 mg/mL should be given via a central catheter; a central catheter is also preferred if repeated or continuous infusion is required. The usual dose is 1 to 1.2 g over 24 hours, given by intermittent or continuous infusion as follows:

- in the UK, an initial infusion of 5 mg/kg in 250 mL of glucose 5% is given over 20 to 120 minutes; the infusion may be repeated if required, up to a total dose of 1.2 g in 24 hours, diluted in up to 500 mL of glucose 5%
- in the USA, an initial dose of 150 mg in 100 mL of glucose 5% is given over 10 minutes, followed by 900 mg in 500 mL of glucose 5% over 24 hours, given at a rate of 1 mg/minute for 6 hours and then 500 micrograms/minute for 18 hours; if necessary the maintenance infusion may be continued at a rate of 500 micrograms/minute using a 1 to 6 mg/mL solution
- In emergencies, amiodarone hydrochloride may be given in doses of 150 to 300 mg in 10 to 20 mL of glucose 5% by slow intravenous injection over a period of not less than 3 minutes; a second injection should not be given until at least 15 minutes after the first

For the use of amiodarone in children, see below.

◊ General references.

1. Goldschlager N, *et al.* Practical guidelines for clinicians who treat patients with amiodarone. *Arch Intern Med* 2000; **160:** 1741–8.
2. Anonymous. Using oral amiodarone safely. *Drug Ther Bull* 2003; **41:** 9–12. Correction. *ibid.*; 40.
3. Siddoway LA. Amiodarone: guidelines for use and monitoring. *Am Fam Physician* 2003; **68:** 2189–96.
4. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007; **298:** 1312–22.

Administration. Addition of amiodarone hydrochloride to an intravenous infusion solution reduces the drop size delivered[1,2] and the reduction in size is greater as the concentration of amiodarone is increased. This resulted[1] in a reduction of about 30% in the expected delivery rate when amiodarone hydrochloride 1.2 g was given in 500 mL of glucose 5%. The reduction in drop size has been attributed to a reduction in surface tension caused by inclusion of Tween 80 (polysorbate 80) in the commercial injection.[1] Allowances should be made for the changes in drop size causing a reduction of the delivery rate of infusions of amiodarone hydrochloride. US licensed product information contra-indicates the use of drop-counter infusion sets and requires the use of a volumetric infusion pump when intravenous amiodarone is given.

1. Capps PA, Robertson AL. Influence of amiodarone injection on the delivery rate of intravenous fluids. *Pharm J* 1985; **234:** 14–15.
2. Chouhan UM, Lynch E. Amiodarone intravenous infusion. *Pharm J* 1985; **235:** 466.

Administration in children. Amiodarone has been used orally and intravenously in infants and children[1-3] although use of the injection is generally contra-indicated in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see Neonates, under Benzyl Alcohol, p.1632) and may cause adverse effects in children up to 3 years old. In the management of cardiac arrhythmias, amiodarone hydrochloride may be given orally in a loading dose of 10 to 20 mg/kg daily (or 500 mg/m^2 daily) for 7 to 10 days, followed by the lowest possible maintenance dose, ranging from 5 to 10 mg/kg daily (or 250 mg/m^2 daily) according to response. It has also been given intravenously in a loading dose of 5 mg/kg given over 20 minutes to 2 hours, followed by a maintenance dose of 10 to 15 mg/kg daily. The *BNFC* suggests intravenous doses of 5 mg/kg given over 30 minutes and repeated every 12 to 24 hours for neonates, and 5 to 10 mg/kg given over 20 minutes to 2 hours and followed by continuous infusion of 300 micrograms/kg per hour (maximum 1.5 mg/kg per hour) for infants and children.

1. Shuler CO, *et al.* Efficacy and safety of amiodarone in infants. *Am Heart J* 1993; **125:** 1430–2.
2. Figa FH, *et al.* Clinical efficacy and safety of intravenous amiodarone in infants and children. *Am J Cardiol* 1994; **74:** 573–7.
3. Saul JP, *et al.* Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation* 2005; **112:** 3470–7.

Advanced cardiac life support. Cardiac arrest should be treated by starting full life support measures (see Advanced Cardiac Life Support, p.1156). Amiodarone may be considered in cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia that is refractory to rapid defibrillation. Although higher doses have been used, guidelines[1-3] now recommend an intravenous dose of 300 mg, with a further dose of 150 mg if necessary; it may be given by intraosseous injection if the intravenous route is not available.[2] In the UK[1] and European guidelines,[3] this may be followed by an infusion of 900 mg over 24 hours. A study[4] in patients with cardiac arrest outside hospital found that amiodarone improved survival to admission, while another study[5] found that it was more effective than lidocaine in this setting. Retrospective studies[6,7] of its use in cardiac arrest occurring in hospital, however, have not found it to be of benefit.

1. Resuscitation Council (UK). Resuscitation Guidelines 2005. Available at: http://www.resus.org.uk/pages/guide.htm (accessed 10/07/07)
2. The American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112:** (suppl 1): IV1–IV203. Available at: http://intl-circ.ahajournals.org/content/vol112/24_suppl/ (accessed 10/07/07)
3. 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 10/07/07)
4. Kudenchuk PJ, *et al.* Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; **341:** 871–8.
5. Dorian P, *et al.* Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; **346:** 884–90. Correction. *ibid.*; **347:** 955.
6. Pollak PT, *et al.* The use of amiodarone for in-hospital cardiac arrest at two tertiary care centres. *Can J Cardiol* 2006; **22:** 199–202.
7. Rea RS, *et al.* Comparing intravenous amiodarone or lidocaine, or both, outcomes for inpatients with pulseless ventricular arrhythmias. *Crit Care Med* 2006; **34:** 1617–23.

Cardiac arrhythmias. Amiodarone is an effective drug for the treatment of symptomatic supraventricular and ventricular arrhythmias[1,2] (p.1160); it has a relatively low risk of cardiovascular adverse effects and may be particularly useful in patients with structural heart disease. It is also used to prevent recurrence of both supraventricular and ventricular arrhythmias, although non-cardiac toxicity may limit its long-term use;[2] a small study[3] suggested that short-term use (4 weeks) delayed the recurrence of atrial fibrillation after electrical cardioversion, but the benefits of this approach require confirmation in larger studies. Amiodarone has been used in children (see above), and has been given by various routes to terminate fetal arrhythmias.[4,5]

Perioperative use[6-8] reduces the incidence of atrial fibrillation and other arrhythmias after cardiac surgery. Amiodarone may also have a role in the management of **cardiac arrest** (see Advanced Cardiac Life Support, above); it has been tried for its antiarrhythmic effect in the management of **heart failure** (see below).

Amiodarone has been used for the prevention of sudden cardiac death in patients with asymptomatic ventricular arrhythmias following myocardial infarction, in patients with a history of aborted sudden cardiac death, and in patients with hypertrophic cardiomyopathy or other cardiac disorders that place them at high risk. Although amiodarone may reduce mortality the effect appears to be small,[2,9,10] and early use of high doses after myocardial infarction may be detrimental.[11] For long-term prophylaxis, implantable cardioverter defibrillators are more effective than antiarrhythmic drugs and are usually preferred; amiodarone may have a role as an adjunct to implantable cardioverter defibrillators to prevent frequent shocks,[12] and may also be used in patients who cannot be given an implantable cardioverter defibrillator.

While amiodarone can cause torsade de pointes it appears to do so rarely[13] and patients who have had this form of ventricular tachycardia as a result of other antiarrhythmic therapy have been given amiodarone subsequently without a recurrence.[14]

1. Desai AD, *et al.* The role of intravenous amiodarone in the management of cardiac arrhythmias. *Ann Intern Med* 1997; **127:** 294–303. Correction. *ibid.* 1998; **128:** 505.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; **100:** 2025–34.
3. Boos C, *et al.* A short course of oral amiodarone improves sinus rhythm maintenance post-cardioversion for atrial fibrillation. *Heart* 2004; **90:** 1063–4.
4. Flack NJ, *et al.* Amiodarone given by three routes to terminate fetal atrial flutter associated with severe hydrops. *Obstet Gynecol* 1993; **82:** 714–16.
5. Strasburger JF, *et al.* Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004; **109:** 375–9.
6. Aasbo JD, *et al.* Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. *Ann Intern Med* 2005; **143:** 327–36.
7. Mitchell LB, *et al.* Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. *JAMA* 2005; **294:** 3093–3100.
8. Khanderia U, *et al.* Amiodarone for atrial fibrillation following cardiac surgery: development of clinical practice guidelines at a university hospital. *Clin Cardiol* 2008; **31:** 6–10.
9. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
10. Hilleman DE, Bauman JL. Role of antiarrhythmic therapy in patients at risk for sudden cardiac death: an evidence-based review. *Pharmacotherapy* 2001; **21:** 556–75.
11. Elizari MV, *et al.* Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. *Eur Heart J* 2000; **21:** 198–205.
12. Connolly SJ, *et al.* Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006; **295:** 165–71.
13. Hohnloser SH, *et al.* Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. *Ann Intern Med* 1994; **121:** 529–35.
14. Mattioni TA, *et al.* Amiodarone in patients with previous drug-mediated torsade de pointes: long-term safety and efficacy. *Ann Intern Med* 1989; **111:** 574–80.

Heart failure. Sudden deaths in patients with severe heart failure (p.1165) have been attributed to ventricular arrhythmias but routine use of antiarrhythmics is not recommended since many have a negative inotropic effect. Amiodarone, which is not a negative inotrope, is usually the drug of choice in patients with heart failure and symptomatic arrhythmias, but its role for prophylaxis is less clear. In the GESICA study (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina)[1] amiodarone appeared to reduce mortality in patients with severe chronic heart failure who were without symptomatic ventricular arrhythmias. The decrease in mortality appeared to be greater than could be expected from antiarrhythmic activity alone. However, in the CHF-STAT study (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure)[2] involving patients with heart failure and premature ventricular contractions, overall survival did not appear to be improved by amiodarone. A meta-analysis[3] including these and 3 further studies concluded that amiodarone reduced the rate of arrhythmic or sudden death in high-risk patients and that this resulted in an overall reduction in mortality. However a further study[4] found that amiodarone had no effect on long-term survival, whereas implantable cardioverter defibrillators reduced mortality by 23%, and a retrospective analysis[5] of a study in patients with heart failure after acute myocardial infarction found that mortality was higher in those taking amiodarone. Although some studies[1,6,7] have suggested that amiodarone may also improve cardiac function, adverse effects limit its use, and it is not currently recommended in heart failure except in patients with symptomatic ventricular arrhythmias.

1. Doval HC, *et al.* Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344:** 493–8.

2. Singh SN, *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; **333:** 77–82.
3. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–24.
4. Bardy GH, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–37.
5. Thomas KL, *et al.* Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J* 2008; **155:** 87–93.
6. Takemura K, *et al.* Low-dose amiodarone for patients with advanced heart failure who are intolerant of beta-blockers. *Circ J* 2002; **66:** 441–4.
7. Choo DC, *et al.* Amiodarone rescue therapy for severe decompensated heart failure initially unsuitable for beta-blockers. *J Cardiovasc Pharmacol Ther* 2003; **8:** 187–92.

Preparations

BP 2008: Amiodarone Intravenous Infusion; Amiodarone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Amiocar; Angoten; Asulblan; Atlansil; Coronax; Coronovo; Miodarona; Miotenk; Ritmocardyl; ***Austral.:*** Aratac; Cardinorm; Cordarone X; Rithmik; ***Austria:*** Sedacoron; ***Belg.:*** Cordarone; ***Braz.:*** Amiobal; Amioron†; Ancoron; Angiodarona; Angyton†; Atlansil; Cardicoron; Cor Mio†; Diodarone; Miocoron; Miodarid; Miodaron; ***Canad.:*** Cordarone; ***Chile:*** Atlansil; Cordarone; Ritmocardyl; ***Cz.:*** Amiohexal; Amiokordin; Cordarone; Ritmopuls; Rivodaron; Sedacoron; ***Denm.:*** Cordan; Cordarone; ***Fin.:*** Cordarone; ***Fr.:*** Corbionax; Cordarone; ***Ger.:*** Amiobeta†; Amiod†; Amiodarex; Amiodura; Amiogamma; Amiohexal; Cordarex; Cornaron; Tachydaron†; ***Gr.:*** Angoron; ***Hong Kong:*** Cordarone; Sedacoron; ***Hung.:*** Amiokordin†; Cordarone; Sedacoron; ***India:*** Aldarone†; Cordarone; Eurythmic; ***Indon.:*** Cordarone; Kendaron; Tiaryt; ***Irl.:*** Cordarone X; ***Israel:*** Amiodacore; Procor; ***Ital.:*** Amiodar; Cordarone; ***Jpn:*** Ancaron; ***Malaysia:*** Aratac; Cordarone; ***Mex.:*** Braxan; Cardiorona†; Cordarone; Forken; Keritmon; Sinarona; ***Neth.:*** Cordarone; ***Norw.:*** Cordarone; ***NZ:*** Aratac; Cordarone X; ***Philipp.:*** Cordarone; ***Pol.:*** Amiokordin; Cordarone; Opacorden; ***Port.:*** Corbionax; Cordarone; Miodrone; ***Rus.:*** Amiokordin (Амиокордин); Cardiodarone (Кардиодарон); Cordarone (Кордарон); Rhythmiodarone (Ритмиодарон); Sedacoron (Седакорон); ***S.Afr.:*** Arycor; Cordarone X; Hexarone; ***Singapore:*** Aratac; Cordarone; ***Spain:*** Trangorex; ***Swed.:*** Cordarone; ***Switz.:*** Amiodar; Cordarone; Escodarone; Rivodarone†; ***Thai.:*** Amdarone; Amidarone 200; Aratac; Cordarone; ***Turk.:*** Cordarone; ***UAE:*** Amirone; ***UK:*** Amyben; Cordarone X; ***USA:*** Cordarone; Pacerone; ***Venez.:*** Arycor†; Coradona; Diarona; Eudarona; Novarona; Trangorex.

Amlodipine Besilate *(BANM, rINNM)*

Amlodipiinibesilaatti; Amlodipin Besilat; Amlodipinbesilat; Amlodipin-besylát; Amlodipin-bezilát; Amlodipine, bésilate d'; Amlodipine Besylate *(USAN)*; Amlodipini besilas; Amlodipino besilatas; Besilato de amlodipino; UK-48340-26; UK-48340-11 (amlodipine maleate). 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate monobenzenesulphonate.

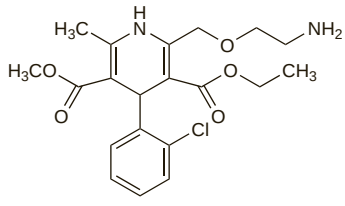
Амлодипина Безилат

$C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$ = 567.1.

CAS — 88150-42-9 (amlodipine); 111470-99-6 (amlodipine besilate); 88150-47-4 (amlodipine maleate).

ATC — C08CA01.

ATC Vet — QC08CA01.



(amlodipine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Amlodipine Besilate). A white or almost white powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in dehydrated alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.
USP 31 (Amlodipine Besylate). A white or almost white powder. Slightly soluble in water and isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Incidence of adverse effects. Of 1091 patients prescribed amlodipine for hypertension, 128 (11.7%) stopped the drug because of adverse effects.[1] The commonest adverse effects were ankle oedema, flushing, headache, skin rash, and fatigue.

1. Benson E, Webster J. The tolerability of amlodipine in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 578P–579P.

Heart failure. Calcium-channel blockers are normally avoided in patients with heart failure but amlodipine has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure receiving the drug.[1] Therefore, it may be a suitable treatment for angina pectoris or hypertension in such patients. However, a study[2] in hypertensive patients (ALLHAT) found that amlodipine was less effective than the diuretic chlortalidone in preventing the development of heart failure.

1. Packer M, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996; **335:** 1107–14.
2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.

Porphyria. Although there have been reports[1,2] of the successful use of amlodipine in patients with porphyria, acute exacerbation has also occurred.[3]

1. Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. *Br J Clin Pharmacol* 1997; **43:** 339–40.
2. Cinemre H, *et al.* Safety of amlodipine use in patients with acute intermittent porphyria. *Br J Clin Pharmacol* 2007; **64:** 246–7.
3. Kepple A, Cernek PK. Amlodipine-induced acute intermittent porphyria exacerbation. *Ann Pharmacother* 1997; **31:** 253.

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Amlodipine is well absorbed after oral doses with peak blood concentrations occurring after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 97.5% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolised in the liver; metabolites are mostly excreted in urine together with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

◊ General reviews.

1. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992; **22:** 22–31.
2. Kang D, *et al.* Population analyses of amlodipine in patients living in the community and patients living in nursing homes. *Clin Pharmacol Ther* 2006; **79:** 114–24.

Absorption. Results of studies involving 24 healthy subjects indicated that absorption of amlodipine from a capsule was equivalent to that from a solution, suggesting that the slow transfer of amlodipine into the blood is a property of the drug not of the dosage form; it was also shown that absorption was not affected by food.[1]

1. Faulkner JK, *et al.* Absorption of amlodipine unaffected by food: solid dose equivalent to solution dose. *Arzneimittelforschung* 1989; **39:** 799–801.

Metabolism. The metabolites of amlodipine have been characterised in *animals* and in human subjects.[1] Metabolism of amlodipine is complex and extensive, and in common with other dihydropyridines oxidation to the pyridine analogue represents a major step. About 5% of a dose was recovered from urine as unchanged amlodipine.

1. Beresford AP, *et al.* Biotransformation of amlodipine. *Arzneimittelforschung* 1989; **39:** 201–9.

Uses and Administration

Amlodipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Amlodipine is given orally as the besilate, but doses are usually expressed in terms of the base; amlodipine besilate 6.9 mg is equivalent to about 5 mg of amlodipine. The camsilate, maleate, and mesilate are also used.

In hypertension the usual initial dose is 5 mg once daily, increased, if necessary, to 10 mg once daily. Similar doses are given in the treatment of stable angina and Prinzmetal's angina. Lower initial doses may be used in elderly patients and those with hepatic impairment (see below).

The (*S*)-isomer of amlodipine besilate has also been used.

◊ Reviews.

1. Murdoch D, Heel RC. Amlodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1991; **41:** 478–505.
2. Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs* 1995; **50:** 560–86.

Administration in children. Amlodipine has been used to reduce blood pressure in children and adolescents with hypertension. In a study[1] in 28 children aged 3 to 19 years, amlodipine 5 to 10 mg (about 200 to 300 micrograms/kg) once daily significantly reduced blood pressure; therapy was withdrawn in 5 patients due to oedema and flushing. Another study[2] in 268 children aged 6 to 16 years found that amlodipine in a dose of 2.5 or 5 mg (ranging from about 20 to 340 micrograms/kg) once daily was well tolerated; doses above 60 micrograms/kg daily significantly reduced blood pressure. Younger children may need higher doses than older children. In a study[3] in 21 patients aged 6 to 17 years, the mean dose required in children under 13 years was 290 micrograms/kg daily compared with 160 micrograms/kg daily for children 13 years and over. Another study[4] in 55 children aged 13 months to 20 years reported similar mean doses, but also found that many of the younger children needed twice daily dosing. Amlodipine was well tolerated in both studies. The need for a higher dose was supported by a pharmacokinetic study,[5] which found that amlodipine clearance was increased in younger children.

1. Pfammatter JP, *et al.* Amlodipine once-daily in systemic hypertension. *Eur J Pediatr* 1998; **157:** 618–21.
2. Flynn JT, *et al.* A randomized, placebo-controlled trial of amlodipine in children with hypertension. *J Pediatr* 2004; **145:** 353–9.
3. Tallian KB, *et al.* Efficacy of amlodipine in pediatric patients with hypertension. *Pediatr Nephrol* 1999; **13:** 304–10.
4. Flynn JT, *et al.* Treatment of hypertensive children with amlodipine. *Am J Hypertens* 2000; **13:** 1061–6.
5. Flynn JT, *et al.* Population pharmacokinetics of amlodipine in hypertensive children and adolescents. *J Clin Pharmacol* 2006; **46:** 905–16.

Administration in hepatic impairment. The clearance of amlodipine is reduced in patients with hepatic impairment and lower doses should be considered; an initial dose of 2.5 mg once daily has been recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Abloom; Amloc; Amlodine; Amlotens; Amze; Anexa; Angiofilina; Angipec; Arteriosan; Calpres; Carboplex; Cardiorex; Cardivas; Coroval; Dronalden; Hipertensal; Ilduc; Mitokor; Nexotensil; Nikor; Pelmec; Sinop†; Terloc; Tervalon; Zundic; ***Austral.:*** Norvasc; Perivasc; ***Austria:*** Amlodanorm; Amloreg; Norvasc; ***Belg.:*** Amlogal; Amlor; ***Braz.:*** Amilopil; Amlocor; Amloprax†; Amlovasc†; Anlo; Anlodibal; Cordarex; Cordipina; Lodipen†; Lodipil; Nemodine†; Nicord; Norvasc; Pressat; Roxflan; Tensaliv; Tensodin; ***Canad.:*** Norvasc; ***Chile:*** Amdipin; Amloc; Avirin†; Norvasc; Presilam; Presovasc; Terloc; ***Cz.:*** Afiten; Agen; Alozur; Amilostad; Amlodigamma; Amlopp; Amlotenz; Amlozek; Apo-Amlo; Cardilopin; Genam; Hipres; Normodipine; Norvasc; Orcal; Recotens; Tensigal; Torella; Zeppeliton; Zorem; Zufalm; ***Denm.:*** Norvasc; ***Fin.:*** Norvasc; ***Fr.:*** Amlor; ***Ger.:*** Amlo Tad; Amlo Wolff; Amlo-corax; Amlo-Isis; Amlo-Q; Amlobeta; Amlocard; Amloclair; Amlodigamma; Amlodoc; AmloLich; Amparo; Norvasc; ***Gr.:*** Aggovask; Amlibon; Amlodil; Amlopen; Amlopress; Amloretin; Amlosilat; Amlotens; Amodipan; Baruden; Dafor; Evangio; Flodil; Hypertel; Kaprin; Lodipin; Naxuril; Nolvac; Nordex; Norfan; Normodin; Norvasc; Precardin; Ramlet; Rovoxid; Vascodin; ***Hong Kong:*** Norvasc; ***Hung.:*** Agen; Amlodep; Amlodigamma; Amlodowin; Amlozek; Cardilopin; Normodipine; Norvasc; Tenox; ***India:*** Amdepin; Amlodac; Amlogard; Amlopres; Amlosafe†; Amlostat; Amlotrust; Calchek; Lama; Myodura; S-Amlip; ***Indon.:*** Amdixal; Norvask; Tensivask; ***Irl.:*** Amlid; Amlist; Amlode; Istin; Myostin; ***Israel:*** Amlow; Norvasc; ***Ital.:*** Antacal; Monopina; Norvasc; ***Jpn:*** Amlodin; Norvasc; ***Malaysia:*** Nordipine; Norvasc; Sunvasc; Vamlo; ***Mex.:*** Amlibon; Nexus; Norvas; Oralcam; ***Neth.:*** Amlo; Amlonor; Amlostad; Amlosyl; Norvasc; ***Norw.:*** Norvasc; ***NZ:*** Calvasc; Norvasc; ***Philipp.:*** Norvasc; ***Pol.:*** Aldan; Amlopin; Amloratio; Amlozek; Apo-Amlo; Cardilopin; Normodipine; Norvasc; Suplar; Tenox; Vilpin; ***Port.:*** Cardionox; Corpress†; Famonor; Ibotec; Mibral; Monodin; Nivelcor†; Norvasc; Tiflodipine; ***Rus.:*** Akridipin (Акридипин); Amlodil (Амлодил); Amlotop (Амлотоп); Amlovas (Амловас); Calchek (Калчек); Cardilopin (Кардилопин); Corvadil (Корвадил); Normodipine (Нормодипин); Norvasc (Норваск); Omelar Cardio (Омелар Кардио); ***S.Afr.:*** Amlate; Amloc; Amlosyn; Norvasc; ***Singapore:*** Norvasc; ***Spain:*** Amlodeq†; Amlor; Amlotabs†; Astudal; Kerniox; Norvas; Presdeten; ***Swed.:*** Norvasc; ***Switz.:*** Alzar; Amlo eco; Amlopin; Amlovasc; Norvasc; ***Thai.:*** Amlopine; Deten; Lovas; Norvasc; ***Turk.:*** Amlodis; Amlokard; Amlovas; Biocard; Dilopin; Monovas; Nipidol; Norlopin; Normopres; Norvadin; Norvasc; Vasocard; Vazkor; ***UK:*** Amlostin; Istin; ***USA:*** Amvaz†; Norvasc; ***Venez.:*** Amlibon; Amlip; Amloc†; Amlopin; Amlovas; Angiovan; Dilotex; Lodipin; Nilan†; Norvasc; Pinam; Stamlo†; Unidoscor†.

Multi-ingredient: ***Arg.:*** Adrebloc†; Amlopril; Amzepril†; Arteriosan Plus; Coroval B; Diovan A; Diovan Triple; Hipertensal Combi; Ilduc Duo; Lipoarteriosan; Pelmec Duo; Terloc Duo; ***Austral.:*** Caduet; ***Braz.:*** Atmos; Betalor; Caduet; Diovan Amlo; Naprix A; Sinergen; ***Chile:*** Caduet; ***Cz.:*** Caduet; Copalia; Dafiro; Exforge; Imprida; ***Fr.:*** Caduet; ***Gr.:*** Copalia; Dafiro; Exforge; ***Hung.:*** Caduet; Lisonorm; ***India:*** Alsartan-AM; Amace-BP; Amdepin-AT; Amlopres AT; Amlopres L; Amlopres Z; Amlosafe-AT†; Amlosafe-LS†; Amlostat-AT; Biopril-AM†; Calchek L; Dilvas AM; Tenochek; Tenolol-AM; ***Malaysia:*** Caduet; ***Mex.:*** Amlidual; Caduet; ***Philipp.:*** Envacar; ***Port.:*** Caduet; Copalia; Dafiro; Imprida; ***Rus.:*** Ampliton (Амплитон); Tenochek (Теночек); ***S.Afr.:*** Caduet; ***Singapore:*** Caduet; ***UK:*** Exforge; ***USA:*** Azor; Caduet; Exforge; Lotrel; ***Venez.:*** Amlibon B; Caduet; Diovan/Amlibon; Duopres.