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.

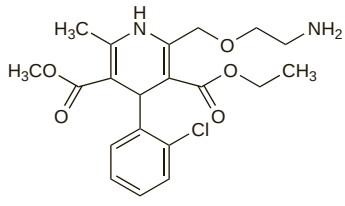
Амлодипина Безилат

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

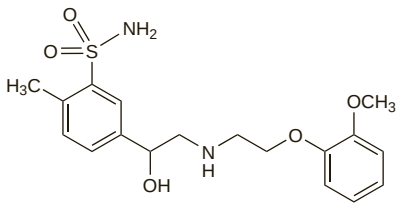
Amosulalol Hydrochloride *(rINNM)* ⊗

Amosulalol, Chlorhydrate d'; Amosulaloli Hydrochloridum; Hidrocloruro de amosulalol; YM-09538. (±)-5-(1-Hydroxy-2-{[2-(*o*-methoxyphenoxy)ethyl]amino}ethyl)-*o*-toluenesulphonamide hydrochloride.

Амосулалола Гидрохлорид

$C_{18}H_{24}N_2O_5S,HCl$ = 416.9.

CAS — 85320-68-9 (amosulalol); 70958-86-0 (amosulalol hydrochloride); 93633-92-2 (amosulalol hydrochloride).



(amosulalol)

Profile

Amosulalol is a beta blocker (p.1225); it also has alpha-blocking activity. It has been given orally as the hydrochloride in the management of hypertension.

Amrinone *(BAN, rINN)*

Amrinon; Amrinona; Amrinoni; Amrinonum; Inamrinone *(USAN)*; Win-40680. 5-Amino-3,4′-bipyridyl-6(1*H*)-one.

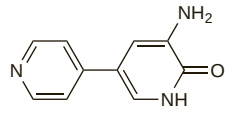
Амринон

$C_{10}H_9N_3O$ = 187.2.

CAS — 60719-84-8.

ATC — C01CE01.

ATC Vet — QC01CE01.



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

USP 31 (Inamrinone). A pale yellow to tan powder; odourless or with a faint odour. Practically insoluble in water and in chloroform; slightly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Amrinone Lactate *(BANM, rINNM)*

Amrinone, Lactate d'; Amrinoni Lactas; Lactato de amrinona.

Амринона Лактат

$C_{10}H_9N_3O,C_3H_6O_3$ = 277.3.

CAS — 75898-90-7.

ATC — C01CE01.

ATC Vet — QC01CE01.

Incompatibility. The manufacturer has reported that amrinone lactate injection is physically incompatible with glucose-containing solutions and with furosemide.

Precipitation occurred[1] when amrinone was mixed with sodium bicarbonate injection, probably because of the reduced solubility of amrinone in alkaline solutions.

1. Riley CM, Junkin P. Stability of amrinone and digoxin, procainamide hydrochloride, propranolol hydrochloride, sodium bicarbonate, potassium chloride, or verapamil hydrochloride in intravenous admixtures. *Am J Hosp Pharm* 1991; **48:** 1245–52.

Adverse Effects

Amrinone produces gastrointestinal disturbances that may necessitate withdrawal of treatment. It produces dose-dependent thrombocytopenia. Hepatotoxicity may occur, particularly during long-term oral treatment. Hypotension and cardiac arrhythmias have been reported. Other adverse effects include headache, fever, chest pain, nail discoloration, and decreased tear production. Hypersensitivity reactions including myositis and vasculitis have been reported. Local pain and burning may occur at the site of intravenous injection.

The adverse effects associated with oral use have made this route unacceptable and amrinone is now only given intravenously for short-term use. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can increase the mortality rate.

◊ References.

1. Wynne J, *et al.* Oral amrinone in refractory congestive heart failure. *Am J Cardiol* 1980; **45:** 1245–9.
2. Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; **49:** 447–51.
3. Wilmshurst PT, *et al.* The effects of amrinone on platelet count, survival and function in patients with congestive cardiac failure. *Br J Clin Pharmacol* 1984; **17:** 317–24.
4. Silverman BD, *et al.* Clinical effects and side effects of amrinone: a study of 24 patients with chronic congestive heart failure. *Arch Intern Med* 1985; **145:** 825–9.
5. Webster MWI, Sharpe DN. Adverse effects associated with the newer inotropic agents. *Med Toxicol* 1986; **1:** 335–42.
6. Mattingly PM, *et al.* Pancytopenia secondary to short-term, high-dose intravenous infusion of amrinone. *DICP Ann Pharmacother* 1990; **24:** 1172–4.
7. Ross MP, *et al.* Amrinone-associated thrombocytopenia: pharmacokinetic analysis. *Clin Pharmacol Ther* 1993; **53:** 661–7.

Precautions

Amrinone should be used with caution in severe obstructive aortic or pulmonary valvular disease or in hypertrophic cardiomyopathy. Blood pressure and heart rate should be monitored during parenteral use. The fluid and electrolyte balance should be maintained. Platelet counts and liver function should also be monitored.

Pharmacokinetics

Although amrinone is rapidly absorbed from the gastrointestinal tract it is no longer given orally. The half-life is variable and after intravenous injection has been reported to be about 4 hours in healthy subjects and about 6 hours in patients with heart failure. Binding to plasma proteins is generally low. Amrinone is partially metabolised in the liver and excreted in the urine as unchanged drug and metabolites; up to about 40% is excreted as unchanged drug after intravenous use. About 18% of an oral dose has been detected in the faeces over 72 hours.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).

Infants. For reference to the pharmacokinetics of amrinone in neonates and infants, see under Uses and Administration, below.

Renal impairment. Studies in a child with multi-organ failure and anuria[1] and in 3 adults with anuria after cardiac surgery[2] have shown that amrinone is effectively removed by haemofiltration but clearance varies widely between patients. Non-renal clearance may also be altered in critically ill patients and monitoring of plasma-amrinone concentrations has been suggested.[2]

1. Lawless S, *et al.* Effect of continuous arteriovenous haemofiltration on pharmacokinetics of amrinone. *Clin Pharmacokinet* 1993; **25:** 80–2.
2. Hellinger A, *et al.* Elimination of amrinone during continuous veno-venous haemofiltration after cardiac surgery. *Eur J Clin Pharmacol* 1995; **48:** 57–9.

Uses and Administration

Amrinone is a phosphodiesterase inhibitor that has vasodilator and positive inotropic properties. It is used in the management of heart failure (p.1165). Although amrinone is effective when given orally this route has been associated with an unacceptable level of adverse effects, and the drug is now only given intravenously for the short-term management of heart failure unresponsive to other forms of therapy.

The mode of action is not fully known, but appears to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increased contractile force in cardiac muscle.

Amrinone is given intravenously as the lactate and doses are expressed in terms of the base. Amrinone lactate 1.48 mg is equivalent to about 1 mg of amrinone. The initial loading dose is 750 micrograms/kg by slow intravenous injection over 2 to 3 minutes. This is followed by a maintenance infusion, although the loading dose may be repeated after 30 minutes if necessary. Maintenance doses are 5 to 10 micrograms/kg per minute by infusion to a usual maximum total dose (including loading doses) of 10 mg/kg in 24 hours. Doses of up to 18 mg/kg daily have been used for short periods in a limited number of patients.

Administration in infants. Pharmacokinetic and pharmacodynamic studies[1,2] in infants undergoing cardiac surgery indicated that the dose needed for infants to achieve a plasma-amrinone concentration of 2 to 7 micrograms/mL was an initial intravenous bolus of 3 to 4.5 mg/kg in divided doses followed by a continuous infusion of 10 micrograms/kg per minute. Neonates appear to eliminate amrinone more slowly than infants, possibly due to their immature renal function;[1,3] it was therefore suggested[1] that neonates should receive a similar bolus dose to infants, followed by a continuous infusion of 3 to 5 micrograms/kg per minute. In a further study[4] that included mainly infants and older children, amrinone clearance and volume of distribution varied widely between patients but did not appear to be related to age.

1. Lawless S, *et al.* Amrinone in neonates and infants after cardiac surgery. *Crit Care Med* 1989; **17:** 751–4.
2. Lawless ST, *et al.* The acute pharmacokinetics and pharmacodynamics of amrinone in pediatric patients. *J Clin Pharmacol* 1991; **31:** 800–3.
3. Laitinen P, *et al.* Pharmacokinetics of amrinone in neonates and infants. *J Cardiothorac Vasc Anesth* 2000; **14:** 378–82.
4. Allen-Webb EM, *et al.* Age-related amrinone pharmacokinetics in a pediatric population. *Crit Care Med* 1994; **22:** 1016–24.

Preparations

USP 31: Inamrinone Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Wincoram†; ***Ger.:*** Wincoram†; ***India:*** Amicor; Cardiotone†; ***Israel:*** Inocor; ***Ital.:*** Inocor†; ***Jpn:*** Amcoral†; Cartonic†; ***Malaysia:*** Inocor†; ***Mex.:*** Inocor; ***Port.:*** Inocor†; ***Spain:*** Wincoram†; ***USA:*** Inocor.

Ancrod *(BAN, USAN, rINN)*

Ancrodum.

Анкрод

CAS — 9046-56-4.

ATC — B01AD09.

ATC Vet — QB01AD09.

Description. Ancrod is an enzyme obtained from the venom of the Malayan pit-viper (*Calloselasma rhodostoma* = *Agkistrodon rhodostoma*).

Adverse Effects and Treatment

Haemorrhage may occur during treatment with ancrod and usually responds to its withdrawal. If haemorrhage is severe, cryoprecipitate can be used to raise plasma fibrinogen concentrations; plasma may be used if cryoprecipitate is not available. An antivenom has been used to neutralise ancrod.

Skin rash, transient chills, and fever have been reported with the use of ancrod.

Precautions

As for Heparin, p.1303.

Ancrod should not be given to patients with severe infections or disseminated intravascular coagulation. It should be used cautiously in patients with cardiovascular disorders that may be complicated by defibrination. It is very important that when ancrod is given by intravenous infusion it should be given slowly to prevent the formation of large amounts of unstable fibrin.

Ancrod is not recommended during pregnancy; high doses in *animals* have caused placental haemorrhage and fetal death.

Interactions

Ancrod should not be used with antifibrinolytics such as aminocaproic acid or with plasma volume expanders such as dextrans.

Uses and Administration

Ancrod is an anticoagulant. It reduces the blood concentration of fibrinogen by the cleavage of microparticles of fibrin which are rapidly removed from the circulation by fibrinolysis or phagocytosis. It reduces blood viscosity but has no effect on established thrombi. Haemostatic concentrations of fibrinogen are normally restored in about 12 hours and normal concentrations in 10 to 20 days.

Ancrod has been used in the treatment of thromboembolic disorders, particularly in deep-vein thrombosis and to prevent thrombosis after surgery in patients requiring anticoagulation but who have developed heparin-induced thrombocytopenia or thrombosis (see Venous Thromboembolism, p.1189). It is under investigation in the treatment of ischaemic stroke and has also been given for priapism.

◊ References.

1. Sherman DG, *et al.* Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *JAMA* 2000; **283:** 2395–2403.
2. Hennerici MG, *et al.* ESTAT investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet* 2006; **368:** 1871–8.