Aliskiren is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4 but few significant interactions have been reported. Plasma-aliskiren concentrations may be reduced by irbesartan and increased by atorvastatin and ketoconazole but the clinical relevance is not clear. Aliskiren has caused significant decreases in furosemide concentrations.

Pharmacokinetics

Aliskiren is poorly absorbed from the gastrointestinal tract with a bioavailability of about 2.5%. Peak plasma concentrations are reached about 1 to 3 hours after an oral dose. Absorption is reduced when aliskiren is taken with a high-fat meal. Aliskiren is about 50% bound to plasma proteins. It is excreted mainly in the faeces, possibly via the bile; about 25% of the absorbed dose is excreted in the urine as unchanged drug. Aliskiren is a substrate for the cytochrome P450 isoenzyme CYP3A4 but metabolism appears to be minimal. The elimination half-life is about 24 to 40 hours, and steady-state concentrations are reached in about 7 to 8 days.

Uses and Administration

Aliskiren is an orally active renin inhibitor used in the management of hypertension; it prevents the conversion of angiotensinogen into angiotensin I and therefore inhibits the production of angiotensin II and aldosterone. It is given as the fumarate, although licensed product information in some countries specifies the base. Doses are expressed in terms of the base; 165.8 mg of aliskiren fumarate is equivalent to about 150 mg of aliskiren. The usual initial oral dose of aliskiren is 150 mg once daily, increased to 300 mg once daily if necessary. Doses may be taken before or after food, but patients should establish a routine pattern with regard to meals.

Aliskiren is also under investigation in heart failure and diabetic nephropathy.

◊ Reviews.

1. Van Tassell BW, Munger MA. Aliskiren for renin inhibition: a new class of antihypertensives. *Ann Pharmacother* 2007; **41:** 456–64.
2. Frampton JE, Curran MP. Aliskiren: a review of its use in the management of hypertension. *Drugs* 2007; **67:** 1767–92.
3. Chrysant SG. Aliskiren-hydrochlorothiazide combination for the treatment of hypertension. *Expert Rev Cardiovasc Ther* 2008; **6:** 305–14.
4. Jensen C, *et al.* Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov* 2008; **7:** 399–410.
5. Sureshkumar KK, *et al.* Aliskiren: clinical experience and future perspectives of renin inhibition. *Expert Opin Pharmacother* 2008; **9:** 825–37.
6. Kappert K, *et al.* Aliskiren. *Dtsch Med Wochenschr* 2008; **133:** 1308–12.

Preparations

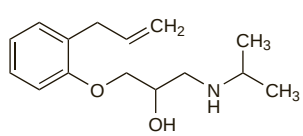
Proprietary Preparations (details are given in Part 3)
Cz.: Enviage; Rasilez; Riprazo; Sprimeo; Tekturna; ***Fr.:*** Rasilez; ***Port.:*** Enviage; Rasilez; Riprazo; Tekturna; ***UK:*** Rasilez; ***USA:*** Tekturna.

Alprenolol *(BAN, rINN)* ⊗

Alprénolol; Alprenololi; Alprenololum. 1-(2-Allylphenoxy)-3-isopropylaminopropan-2-ol.

Алпренолол

$C_{15}H_{23}NO_2$ = 249.3.
CAS — 13655-52-2.
ATC — C07AA01.
ATC Vet — QC07AA01.



Alprenolol Benzoate *(BANM, rINNM)* ⊗

Alprénolol, benzoate d'; Alprenololi benzoas; Benzoato de alprenolol.

Алпренолола Бензоат

$C_{22}H_{29}NO_4$ = 371.5.
ATC — C07AA01.
ATC Vet — QC07AA01.

Alprenolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Alprénolol, chlorhydrate d'; Alprenolol-hidroklorid; Alprenolol-hydrochlorid; Alprenololhydroklorid; Alprenololi hydrochloridum; Alprenololihydrokloridi; Alprenololio hidrochloridas; H56/28; Hidrocloruro de alprenolol.

Алпренолола Гидрохлорид

$C_{15}H_{23}NO_2$,HCl = 285.8.
CAS — 13707-88-5.
ATC — C07AA01.
ATC Vet — QC07AA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Alprenolol Hydrochloride). A white, or almost white, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Alprenolol is a non-cardioselective beta blocker (p.1225). It is reported to have intrinsic sympathomimetic activity and some membrane-stabilising properties.

Alprenolol has been given orally, as the benzoate or hydrochloride, in the management of hypertension, angina pectoris, and cardiac arrhythmias.

Alteplase *(BAN, USAN, rINN)*

Alteplaasi; Alteplas; Alteplasa; Altéplase; Alteplasum; Alteplaz; G-11035; G-11044; G-11021 (2-chain form); Recombinant Tissue-type Plasminogen Activator; rt-PA.

Альтеплаза

CAS — 105857-23-6.
ATC — B01AD02; S01XA13.
ATC Vet — QB01AD02; QS01XA13.

Description. Alteplase is a glycosylated protein of 527 residues having the amino acid sequence of human tissue plasminogen activator (t-PA) and produced by recombinant DNA technology.

Pharmacopoeias. In *US. Eur.* (see p.vii) includes Alteplase for Injection.
Ph. Eur. 6.2 (Alteplase for Injection; Alteplasum ad Iniectabile). A sterile, freeze-dried preparation of alteplase, a tissue plasminogen activator produced by recombinant DNA technology. It has a potency of not less than 500 000 units/mg of protein. It is a white or slightly yellow powder or friable mass. The reconstituted preparation has a pH of 7.1 to 7.5. Store in colourless glass containers, under vacuum or an inert gas, at a temperature between 2° and 30°. Protect from light. Alteplase consists of 527 amino acids with carbohydrate moieties attached.
USP 31 (Alteplase). A highly purified glycosylated serine protease with fibrin-binding properties and plasminogen-specific proteolytic activities. It is produced by recombinant DNA synthesis in mammalian cell culture. It has a potency of 522 000 to 667 000 USP units/mg of protein. Store in airtight containers in the frozen state at a temperature of –20° or below.

Incompatibility and stability. Alteplase has been reported[1] to be incompatible with dobutamine, dopamine, glyceryl trinitrate, and heparin, although a subsequent study found no incompatibility between alteplase and glyceryl trinitrate.[2] Another study[3] found that dilution of a proprietary preparation of alteplase (Activase) to 0.09 and 0.16 mg/mL with glucose 5% resulted in precipitation of the drug. Alteplase is formulated with arginine as a solubilising agent, and dilution with glucose 5% to concentrations below 0.5 mg/mL of alteplase makes precipitation possible. Dilution with sodium chloride 0.9% is possible to concentrations down to 0.2 mg/mL before precipitation becomes a risk.

Studies[4,5] have suggested that a 1 mg/mL solution of alteplase retains its activity when frozen at –20° or below for up to 6 months.

1. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
2. Lam XM, *et al.* Stability and activity of alteplase with injectable drugs commonly used in cardiac therapy. *Am J Health-Syst Pharm* 1995; **52:** 1904–9.
3. Frazin BS. Maximal dilution of Activase. *Am J Hosp Pharm* 1990; **47:** 1016.
4. Calis KA, *et al.* Bioactivity of cryopreserved alteplase solutions. *Am J Health-Syst Pharm* 1999; **56:** 2056–7.
5. Wiernikowski JT, *et al.* Stability and sterility of recombinant tissue plasminogen activator at −30°C. *Lancet* 2000; **355:** 2221–2.

Units

The activity of alteplase can be measured in terms of international units using the third International Standard for tissue plasminogen activator recombinant, human, established in 1999, although doses are generally expressed by weight.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Allergic reactions are less likely with alteplase than with streptokinase and repeated use may be possible.

Hypersensitivity. An anaphylactoid reaction to alteplase occurred in a patient with a history of atopy.[1] For comment on this unexpected reaction, see Hypersensitivity under Adverse Effects of Streptokinase, p.1404. (See also ACE Inhibitors under Interactions, below).

1. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; **341:** 966–7.

Thrombin generation. Alteplase produces considerable thrombin generation which may result from direct activation of the coagulation system by plasmin or by positive feedback of the coagulation system by clot-bound thrombin. This excessive thrombin generation was considered a possible cause of myocardial infarction in a patient undergoing thrombolytic therapy with alteplase for venous thrombosis.[1] Streptokinase produced no evidence of excessive thrombin generation.

1. Baglin TP, *et al.* Thrombin generation and myocardial infarction during infusion of tissue-plasminogen activator. *Lancet* 1993; **341:** 504–5.

Interactions

As for Streptokinase, p.1404.

ACE inhibitors. Angioedema has been reported rarely in patients treated with alteplase, but the risk may be increased in those taking ACE inhibitors. A prospective study[1] found that out of 176 patients treated with alteplase for acute stroke, 9 developed angioedema; the risk was strongly associated with use of an ACE inhibitor (7 of the 9).

1. Hill MD, *et al.* Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology* 2003; **60:** 1525–7.

Glyceryl trinitrate. Although thrombolytics and nitrates are both frequently used in acute myocardial infarction a report suggested that this combination may result in impaired thrombolysis. Giving alteplase and glyceryl trinitrate intravenously to 36 patients with acute myocardial infarction produced lower plasma-antigen concentrations of tissue-plasminogen activator than alteplase given alone to 11 patients.[1] Reperfusion was sustained in only 44% of patients receiving both drugs compared with 91% of patients given alteplase alone. The authors of a subsequent study[2] suggested that these lower plasma concentrations may be due to increased hepatic metabolism of alteplase as a result of glyceryl trinitrate's effect of increasing hepatic blood flow.

1. Nicolini FA, *et al.* Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 1994; **74:** 662–6.
2. Romeo F, *et al.* Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* 1995; **130:** 692–7.

Pharmacokinetics

Alteplase is cleared rapidly from the plasma, mainly by metabolism in the liver. It has an initial half-life of 4 to 5 minutes and a terminal half-life of about 40 minutes.

◊ References.

1. Krause J. Catabolism of tissue-type plasminogen activator (t-PA), its variants, mutants and hybrids. *Fibrinolysis* 1988; **2:** 133–42.

Uses and Administration

Alteplase is a thrombolytic drug. It is a mainly single-chain form of the endogenous enzyme tissue plasminogen activator and is produced by recombinant DNA technology. Like endogenous tissue plasminogen activator, alteplase converts fibrin-bound plasminogen to the active form plasmin, resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Alteplase has relatively little effect on circulating, unbound plasminogen and thus may be termed a fibrin-specific thrombolytic (see p.1156).

Alteplase is used similarly to streptokinase (p.1404) in the treatment of thromboembolic disorders, particularly myocardial infarction (p.1175) and venous thromboembolism (p.1189), and to clear occluded catheters (see below). Alteplase may also be used in patients with acute ischaemic stroke (p.1185).

In the treatment of acute **myocardial infarction**, alteplase is given intravenously as soon as possible after the onset of symptoms in a total dose of 100 mg; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The total dose may be given either over 1½ hours (accelerated or 'front-loaded' al-

teplase) or over 3 hours. The accelerated schedule has been recommended if given within 6 hours of myocardial infarction, while the 3-hour schedule has been recommended when used more than 6 hours after myocardial infarction. The schedule over 1½ hours is as follows: 15 mg as an intravenous bolus, then 0.75 mg/kg, up to a maximum of 50 mg, by intravenous infusion over 30 minutes, followed by the remainder infused over the subsequent 60 minutes. The schedule over 3 hours is as follows: 10 mg as an intravenous bolus, then 50 mg by intravenous infusion over 1 hour, followed by the remainder infused over the subsequent 2 hours.

In the treatment of acute, massive **pulmonary embolism** a total dose of 100 mg is given; the total dose should not exceed 1.5 mg/kg in patients weighing less than 65 kg. The first 10 mg is given as an intravenous bolus and the remainder by intravenous infusion over 2 hours.

In acute **ischaemic stroke**, alteplase is given within 3 hours of the onset of symptoms in a dose of 0.9 mg/kg up to a maximum total dose of 90 mg. The dose is given intravenously over 60 minutes with 10% of it as a bolus during the first minute.

To **restore function in central venous lines,** alteplase is instilled into the catheter at a concentration of 1 mg/mL. The usual dose is 2 mg, repeated after 2 hours if necessary. A total dose of 4 mg should not be exceeded. For patients weighing less than 30 kg, the dose is 110% of the internal lumen volume of the catheter, but should not exceed 2 mg, and may be repeated after 2 hours if necessary.

◊ General references.

1. Gillis JC, *et al.* Alteplase: a reappraisal of its pharmacological properties and therapeutic use in acute myocardial infarction. *Drugs* 1995; **50:** 102–36.
2. Wagstaff AJ, *et al.* Alteplase: a reappraisal of its pharmacology and therapeutic use in vascular disorders other than acute myocardial infarction. *Drugs* 1995; **50:** 289–316.
3. Semba CP, *et al.* Society of Cardiovascular and Interventional Radiology (SCVIR). Alteplase and tenecteplase: applications in the peripheral circulation. *Tech Vasc Interv Radiol* 2001; **4:** 99–106.
4. Lindley RI, *et al.* Alteplase and ischaemic stroke: have new reviews of old data helped? *Lancet Neurol* 2005; **4:** 249–53.
5. De Keyser J, *et al.* Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke* 2007; **38:** 2612–8.
6. Quinn TJ, *et al.* Past, present and future of alteplase for acute ischemic stroke. *Expert Rev Neurother* 2008; **8:** 181–92.

Arterial and venous thromboembolism. For the use of alteplase for arterial or venous thromboembolism in children, see Administration in Children under Streptokinase, p.1405.

Catheters and cannulas. Alteplase has been used successfully to clear thrombi in central venous catheters.[1,2] Typical doses have been 2 mg injected as a bolus into the blocked catheter. Children have been treated similarly; in one study[3] where patients' weight started from 3 kg, doses ranged from 0.1 to 2.0 mg (as a 1 mg/mL solution), depending on the size of the catheter. Similarly, a later study using a 1 mg/mL solution gave doses of 2 mg to children weighing 30 kg or more, and a volume equal to 110% of the calculated internal volume of the catheter (rounded to the nearest 0.1 mL and not to exceed 2 mL in total) in children weighing less than 30 kg.[4] The dwell time was up to 2 hours, and doses were repeated once in patients in whom catheter function was not restored after this period. A cohort study[5] used doses of 0.5 mg for children weighing 10 kg or under, and 1 to 2 mg above this weight, with a dwell time of 2 to 4 hours. In another report, 2 children[6] were successfully treated with intravenous alteplase in doses of 0.01 to 0.05 mg/kg per hour for venous thrombosis associated with indwelling intravascular catheters.

Alteplase has also been instilled into central haemodialysis lines to preserve patency between dialysis sessions.[7] Urokinase has been used similarly in children with long-term venous access devices for antineoplastic therapy.[8]

For reports covering the use of alteplase to treat intracardiac thrombosis resulting from the placement of central venous lines, see Intracardiac Thrombosis, below.

1. Paulsen D, *et al.* Use of tissue plasminogen activator for reopening of clotted dialysis catheters. *Nephron* 1993; **64:** 468–9.
2. Haire WD, *et al.* Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. *Thromb Haemost* 1994; **72:** 543–7.
3. Jacobs BR, *et al.* Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001; **139:** 593–6.
4. Blaney M, *et al.* CAPS Investigators. Alteplase for the treatment of central venous catheter occlusion in children: results of a prospective, open-label, single-arm study (The Cathflo Activase Pediatric Study). *J Vasc Interv Radiol* 2006; **17:** 1745–51.
5. Choi M, *et al.* The use of alteplase to restore patency of central venous lines in pediatric patients: a cohort study. *J Pediatr* 2001; **139:** 152–6.
6. Doyle E, *et al.* Thrombolysis with low dose tissue plasminogen activator. *Arch Dis Child* 1992; **67:** 1483–4.
7. Gittins NS, *et al.* Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Arch Dis Child* 2007; **92:** 499–501.
8. Dillon PW, *et al.* Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. *J Clin Oncol* 2004; **22:** 2718–23.

Intracardiac thrombosis. Alteplase has been used, in a dose of 100 mg given intravenously over 2 hours, for thrombosis of prosthetic heart valves.[1]

Alteplase has been used successfully in a neonate to treat intracardiac thrombosis associated with the use of a central venous line.[2] A dose of 500 micrograms/kg given over 10 minutes was followed by infusion of 200 micrograms/kg per hour for 3 days. In another report,[3] 4 preterm infants were treated successfully. All received 400 to 500 micrograms/kg of alteplase in a 20 to 30 minute bolus. This was followed in one case by a 3-hour infusion at 100 micrograms/kg per hour.

Although thrombolytics are usually contra-indicated in patients with infective endocarditis (see Precautions for Streptokinase, p.1404), alteplase has been used successfully in children with indwelling catheters who developed infective endocarditis; coagulation was monitored and fresh frozen plasma was given to maintain fibrinogen concentrations.[4]

1. Astengo D, *et al.* Recombinant tissue plasminogen activator for prosthetic mitral-valve thrombosis. *N Engl J Med* 1995; **333:** 259.
2. Van Overmeire B, *et al.* Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator. *Arch Dis Child* 1992; **67:** 443–5.
3. Ferrari F, *et al.* Early intracardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator. *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F66–F69.
4. Levitas A, *et al.* Successful treatment of infective endocarditis with recombinant tissue plasminogen activator. *J Pediatr* 2003; **143:** 649–52.

Microvessel thrombosis. Alteplase has been used in conditions where the underlying pathology is occlusion of small blood vessels by microthrombi.

Purpura and loss of circulation in the hands of a patient recovering from **fulminant meningococcaemia**[1] responded to intra-arterial infusion of alteplase 20 to 40 micrograms/kg per hour for 22 hours in the right hand, and 20 micrograms/kg per hour for 11 hours in the left. Perfusion was successfully restored to both hands, and full function subsequently attained in them. Improvement was also achieved when alteplase was given to 2 infants with septic shock and purpura fulminans caused by meningococcal infection.[2]

Six patients[3] with ulcers caused by **livedoid vasculitis** and refractory to conventional treatment were treated with alteplase 10 mg infused intravenously over 4 hours daily for 14 days. Most ulcers healed rapidly; one patient required re-treatment with concomitant anticoagulation. Healing of ulcers associated with **calciphylaxis** has also been reported[4] with a similar alteplase regimen.

A 4-year-old girl[5] with **haemolytic-uraemic syndrome** (see under Thrombotic Microangiopathies, p.1076) responded to treatment with an intravenous infusion of alteplase 200 micrograms/kg per hour for 5 hours, subsequently reduced to 50 micrograms/kg per hour for 14 days.

Alteplase use has been reviewed[6] and mixed results found, in patients with **veno-occlusive disease of the liver**, a serious complication of bone marrow transplantation that may be caused by diffuse thrombi in the hepatic venules. Although results in patients with established veno-occlusive disease have been disappointing,[7] one study[8] suggested that alteplase given early in the course of the disease improves response rate.

1. Keeley SR, *et al.* Tissue plasminogen activator for gangrene in fulminant meningococcaemia. *Lancet* 1991; **337:** 1359.
2. Zenz W, *et al.* Recombinant tissue plasminogen activator treatment in two infants with fulminant meningococcemia. *Pediatrics* 1995; **96:** 44–8.
3. Klein KL, Pittelkow MR. Tissue plasminogen activator for treatment of livedoid vasculitis. *Mayo Clin Proc* 1992; **67:** 923–33.
4. Sewell LD, *et al.* Low-dose tissue plasminogen activator for calciphylaxis. *Arch Dermatol* 2004; **140:** 1045–8.
5. Kruez W, *et al.* Successful treatment of haemolytic uraemic syndrome with recombinant tissue-type plasminogen activator. *Lancet* 1993; **341:** 1665–6.
6. Terra SG, *et al.* A review of tissue plasminogen activator in the treatment of veno-occlusive liver disease after bone marrow transplantation. *Pharmacotherapy* 1997; **17:** 929–37.
7. Bearman SI, *et al.* Treatment of hepatic venocclusive disease with recombinant human tissue plasminogen activator and heparin in 42 marrow transplant patients. *Blood* 1997; **89:** 1501–6.
8. Schriber J, *et al.* Tissue plasminogen activator (tPA) as therapy for hepatotoxicity following bone marrow transplantation. *Bone Marrow Transplant* 1999; **24:** 1311–14.

Ocular disorders. Intra-ocular alteplase has been used to treat postoperative fibrinous deposits that can form after procedures such as surgery for cataracts[1] or glaucoma,[2] including cataracts in children.[3] Doses ranging from 6 to 25 micrograms have been used. Intra-ocular bleeding has occurred as a complication of such use.[2,4] Alteplase has also been used prophylactically in children undergoing surgery for congenital cataracts.[5]

Intra-ocular alteplase has also been used for treatment of subhyaloid haemorrhage,[6,7] including that seen in shaken baby syndrome.[8] Successful treatment of subretinal macular haemorrhage with alteplase injected directly into the subretinal area around the clot has also been reported.[9]

1. Heiligenhaus A, *et al.* Recombinant tissue plasminogen activator in cases with fibrin formation after cataract surgery: a prospective randomised multicentre study. *Br J Ophthalmol* 1998; **82:** 810–15.
2. Lundy DC, *et al.* Intracameral tissue plasminogen activator after glaucoma surgery: indications, effectiveness, and complications. *Ophthalmology* 1996; **103:** 274–82.
3. Mehta JS, Adams GGW. Recombinant tissue plasminogen activator following paediatric cataract surgery. *Br J Ophthalmol* 2000; **84:** 983–6.
4. Azuara-Blanco A, Wilson RP. Intraocular and extraocular bleeding after intracameral injection of tissue plasminogen activator. *Br J Ophthalmol* 1998; **82:** 1345–6.
5. Siatiri H, *et al.* Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery. *Br J Ophthalmol* 2005; **89:** 1458–61.
6. Schmitz K, *et al.* Therapy of subhyaloidal haemorrhage by intravitreal application of rtPA and SF gas. *Br J Ophthalmol* 2000; **84:** 1324–5.
7. Koh HJ, *et al.* Treatment of subhyaloid haemorrhage with intravitreal tissue plasminogen activator and C F gas injection. *Br J Ophthalmol* 2000; **84:** 1329–30.
8. Conway MD, *et al.* Intravitreal tPA and SF promote clearing of premacular subhyaloid hemorrhages in shaken and battered baby syndrome. *Ophthalmic Surg Lasers* 1999; **30:** 435–41.
9. Singh RP, *et al.* Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. *Br J Ophthalmol* 2006; **90:** 429–31.

Peripheral arterial thromboembolism. Thrombolytics, including alteplase, may be used in the management of peripheral arterial thromboembolism (p.1178). Alteplase has been injected intravenously or intra-arterially directly into the clot as an alternative to surgical treatment of the occlusion. It has also been infused intra-arterially to remove distal clots during a surgical procedure. Alteplase is claimed to produce more rapid thrombolysis than streptokinase although studies have been too small to provide evidence of reduced limb loss or mortality.[1] The most common dose range is 0.5 to 1 mg/hour given *intra-arterially*.[1-3]

An *intravenous* dose of 500 micrograms/kg per hour for the first hour followed by 250 micrograms/kg per hour until clot lysis occurred has been used in infants.[4] Treatment of arterial thrombosis in neonates has been reported, using doses of alteplase ranging from 100 to 500 micrograms/kg per hour *intravenously*.[5,6] The *BNFC* recommends a dose for any intravascular thrombosis in neonates and children of 100 to 500 micrograms/kg per hour by intravenous infusion over 3 to 6 hours; a second dose may be given if needed. The maximum daily dose should not exceed 100 mg. However, a retrospective study[7] of 80 infants and children with arterial or venous thrombi found that although treatment with alteplase may be effective, it is associated with a low safety margin and an unknown risk-benefit ratio.

Where a thrombolytic is used to remove distal clots during a surgical procedure alteplase has been given *intra-arterially* as three doses of 5 mg at 10-minute intervals.[8]

1. Wolfe JH. Critical limb ischaemia. *Prescribers' J* 1994; **34:** 50–8.
2. Anonymous. Non-coronary thrombolysis. *Lancet* 1990; **335:** 691–3.
3. Ward AS, *et al.* Peripheral thrombolysis with tissue plasminogen activator: results of two treatment regimens. *Arch Surg* 1994; **129:** 861–5.
4. Zenz W, *et al.* Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. *Br Heart J* 1993; **70:** 382–5.
5. Weiner GM, *et al.* Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998; **133:** 133–6.
6. Farnoux C, *et al.* Recombinant tissue-type plasminogen activator therapy of thrombosis in 16 neonates. *J Pediatr* 1998; **133:** 137–40.
7. Gupta AA, *et al.* Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001; **139:** 682–8.
8. Chester JF, *et al.* Peroperative t-PA thrombolysis. *Lancet* 1991; **337:** 861–2.

Preparations

USP 31: Alteplase for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Actilyse; ***Austral.:*** Actilyse; ***Austria:*** Actilyse; ***Belg.:*** Actilyse; ***Braz.:*** Actilyse; ***Canad.:*** Activase; Cathflo; ***Chile:*** Actilyse; ***Cz.:*** Actilyse; ***Denm.:*** Actilyse; ***Fin.:*** Actilyse; ***Fr.:*** Actilyse; ***Ger.:*** Actilyse; ***Gr.:*** Actilyse; ***Hong Kong:*** Actilyse; ***Hung.:*** Actilyse; ***India:*** Actilyse; ***Indon.:*** Actilyse; ***Irl.:*** Actilyse; ***Israel:*** Actilyse; ***Ital.:*** Actilyse; ***Jpn:*** Activacin; ***Malaysia:*** Actilyse; ***Mex.:*** Actilyse; ***Neth.:*** Actilyse; ***Norw.:*** Actilyse; ***NZ:*** Actilyse; ***Philipp.:*** Actilyse; ***Pol.:*** Actilyse; ***Port.:*** Actilyse; ***Rus.:*** Actilyse (Актилизе); ***S.Afr.:*** Actilyse; ***Singapore:*** Actilyse; ***Spain:*** Actilyse; ***Swed.:*** Actilyse; ***Switz.:*** Actilyse; ***Thai.:*** Actilyse; ***Turk.:*** Actilyse; ***UK:*** Actilyse; ***USA:*** Activase; ***Venez.:*** Actilyse.

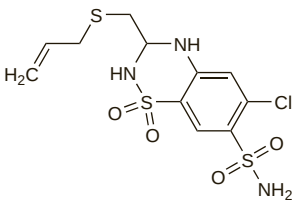
Altizide *(rINN)* ⊗

Althiazide *(USAN)*; Altizida; Altizidum; P-1779. 3-Allylthiomethyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Альтизид

$C_{11}H_{14}ClN_3O_4S_3$ = 383.9.

CAS — 5588-16-9.



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

Ph. Eur. 6.2 (Altizide). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; practically insoluble in dichloromethane. It exhibits polymorphism.

Profile

Altizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that is used in the treatment of oedema and hypertension. It is frequently used with spironolactone.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Aldactazine; ***Fr.:*** Aldactazine; Practazin; Spiroctazine; ***Port.:*** Aldactazine; ***Spain:*** Aldactacine.

Ambrisentan *(BAN, rINN)*

Ambrisentán; Ambrisentanum; BSF-208075; LU-208075. (+)-(2*S*)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

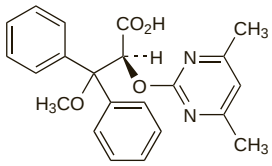
Амбризентан

$C_{22}H_{22}N_2O_4$ = 378.4.

CAS — 177036-94-1.

ATC — C02KX02.

ATC Vet — QC02KX02.



Adverse Effects and Precautions

As for Bosentan, p.1235.

Interactions

Ambrisentan is a substrate for a number of enzymes and transporters and interactions could potentially occur with inducers or inhibitors of the cytochrome P450 isoenzymes CYP3A4 and CYP2C19, P-glycoprotein, uridine diphosphate glucuronosyltransferases, and organic anion transporting polypeptide (OATP).

Pharmacokinetics

Ambrisentan is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after oral doses. It is about 99% bound to plasma proteins. Ambrisentan is excreted mainly by the liver, although the relative contribution of hepatic metabolism and biliary excretion is not known. The terminal elimination half-life is about 15 hours.

Uses and Administration

Ambrisentan is an endothelin receptor antagonist (p.1155) with similar actions to bosentan (p.1235), although it has a higher selectivity for the endothelin ET_A-receptor. It is used in the management of pulmonary hypertension functional class II or III (p.1179). It is given orally in an initial dose of 5 mg once daily; the dose may be increased to 10 mg once daily if tolerated.

◊ References.

1. Galié N, *et al.* Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005; **46:** 529–35.
2. Vatter H, Seifert V. Ambrisentan, a non-peptide endothelin receptor antagonist. *Cardiovasc Drug Rev* 2006; **24:** 63–76.
3. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. *Vasc Health Risk Manag* 2007; **3:** 11–22.
4. Anonymous. Ambrisentan (Letairis) for pulmonary arterial hypertension. *Med Lett Drugs Ther* 2007; **49:** 87–8.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Volibris; ***USA:*** Letairis.

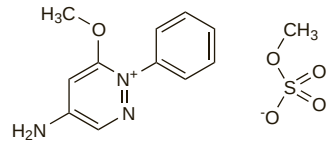
Amezinium Metilsulfate *(rINN)* ⊗

Ametsiniummetilsulfaatti; Amezinii Metilsulfas; Amezinium Methylsulphate; Amézinium, Métilsulfate d'; Ameziniummetilsulfat; Metilsulfato de amezinio. 4-Amino-6-methoxy-1-phenylpyridazinium methylsulfate.

Амезиния Метилсульфат

$C_{12}H_{15}N_3O_5S$ = 313.3.

CAS — 30578-37-1.



Profile

Amezinium metilsulfate is a sympathomimetic (p.1407) used for its vasopressor effects in the treatment of hypotensive states (p.1174). It is given orally in a usual dose of 10 mg up to three times daily. It has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Regulton; ***Ger.:*** Regulton; Supratonin.

Amiloride Hydrochloride

(BANM, USAN, rINNM) ⊗

Amilorid Hidroklorür; Amilorid hydrochlorid dihydrát; Amiloride, chlorhydrate d'; Amilorid-hidroklorid; Amiloridhydroklorid; Amiloridi hydrochloridum; Amiloridi Hydrochloridum Dihydricum; Amiloridihydrokloridi; Amilorido hidrochloridas; Amilorydu chlorowodorek; Amipramizide; Cloridrato de Amilorida; Hidrocloruro de amilorida; MK-870. *N*-Amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate.

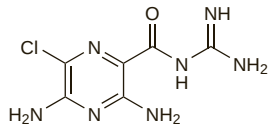
Амилорида Гидрохлорид

$C_6H_8ClN_7O,HCl,2H_2O$ = 302.1.

CAS — 2609-46-3 (amiloride); 2016-88-8 (anhydrous amiloride hydrochloride); 17440-83-4 (amiloride hydrochloride dihydrate).

ATC — C03DB01.

ATC Vet — QC03DB01.



(amiloride)

NOTE. Compounded preparations of amiloride hydrochloride may be represented by the following names:

- Co-amilofruse (*BAN*)—amiloride hydrochloride 1 part and furosemide 8 parts (w/w)
- Co-amilozide (*BAN*)—amiloride hydrochloride 1 part and hydrochlorothiazide 10 parts (w/w)
- Co-amilozide (*PEN*)—amiloride hydrochloride and hydrochlorothiazide.

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

Ph. Eur. 6.2 (Amiloride Hydrochloride). A pale yellow to greenish-yellow powder. Slightly soluble in water and in dehydrated alcohol. Protect from light.

USP 31 (Amiloride Hydrochloride). A yellow to greenish-yellow, odourless or practically odourless, powder. Slightly soluble in water; insoluble in acetone, in chloroform, in ether, and in ethyl acetate; freely soluble in dimethyl sulfoxide; sparingly soluble in methyl alcohol.

Adverse Effects

Amiloride can cause hyperkalaemia, particularly in elderly patients, diabetics, and patients with renal impairment. Hyponatraemia has been reported in patients taking amiloride with other diuretics. Amiloride may cause nausea, vomiting, abdominal pain, diarrhoea or constipation, paraesthesia, thirst, dizziness, skin rash, pruritus, weakness, muscle cramps, headache, and minor psychiatric or visual changes. Orthostatic hypotension and rises in blood-urea-nitrogen concentrations have been reported. Other adverse effects of amiloride may include alopecia, cough, dyspnoea, jaundice, encephalopathy, impotence, angina pectoris, arrhythmias, and palpitations.

Effects on electrolyte balance. There have been reports of metabolic acidosis associated with amiloride or triamterene[1] and with co-amilozide.[2]

1. Kushner RF, Sitrin MD. Metabolic acidosis: development in two patients receiving a potassium-sparing diuretic and total parenteral nutrition. *Arch Intern Med* 1986; **146:** 343–5.
2. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

POTASSIUM. Hyperkalaemia is the main adverse effect when amiloride is given alone but may also occur when amiloride is given with a potassium-wasting diuretic. Severe hyperkalaemia has been reported during co-amilozide therapy, particularly in patients with renal impairment[1,2] and has been accompanied by metabolic acidosis in one such patient.[3]

1. Whiting GFM, *et al.* Severe hyperkalaemia with Moduretic. *Med J Aust* 1979; **1:** 409.
2. Jaffey L, Martin A. Malignant hyperkalaemia after amiloride/hydrochlorothiazide treatment. *Lancet* 1981; **i:** 1272.
3. Wan HH, Lye MDW. Moduretic-induced metabolic acidosis and hyperkalaemia. *Postgrad Med J* 1980; **56:** 348–50.

SODIUM. For reports of severe hyponatraemia in patients taking diuretics such as amiloride with potassium-wasting diuretics, see Hydrochlorothiazide, p.1308.

Effects on the skin. For a report of photosensitivity reactions in patients taking co-amilozide, see Hydrochlorothiazide, p.1309.

Precautions

Amiloride has the same precautions as spironolactone with regard to hyperkalaemia (see p.1400). It should be stopped at least 3 days before glucose-tolerance tests are performed in patients who may have diabetes mellitus because of the risks of provoking severe hyperkalaemia.

Interactions

There is an increased risk of hyperkalaemia if amiloride is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may also occur in patients given amiloride with ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients taking amiloride with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity, but this does not appear to occur with amiloride. Severe hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients taking chlorpropamide. Amiloride may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, amiloride may enhance the effects of other antihypertensive drugs.

Digoxin. For the effects of amiloride on digoxin clearance, see p.1262.

Quinidine. For a report of amiloride producing arrhythmias in patients receiving quinidine, see p.1384.

Pharmacokinetics

Amiloride is incompletely absorbed from the gastrointestinal tract; bioavailability is about 50% and is reduced by food. It is not significantly bound to plasma proteins and has a plasma half-life of 6 to 9 hours; the terminal half-life may be 20 hours or more. It is excreted unchanged by the kidneys.

◊ General references.

1. Weiss P, *et al.* The metabolism of amiloride hydrochloride in man. *Clin Pharmacol Ther* 1969; **10:** 401–6.

Hepatic impairment. In patients with acute hepatitis the terminal half-life of amiloride was 33 hours compared with 21 hours in healthy subjects.[1] The proportion of the dose excreted in the urine was increased from 49 to 80%.

1. Spahn H, *et al.* Pharmacokinetics of amiloride in renal and hepatic disease. *Eur J Clin Pharmacol* 1987; **33:** 493–8.

Renal impairment. Studies of the pharmacokinetics of amiloride[1,2] have reported an increase in terminal elimination half-life from 20 hours in healthy subjects to 100 hours in patients with end-stage renal disease. The natriuretic effect of amiloride was reduced[1] in patients with creatinine clearance below 50 mL/minute. In patients with renal impairment amiloride could aggravate potassium retention due to renal disease. Studies in elderly patients have found increased half-life[3] and steady-state concentrations[4] associated with reduced renal function.

1. Knauf H, *et al.* Limitation on the use of amiloride in early renal failure. *Eur J Clin Pharmacol* 1985; **28:** 61–6.