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

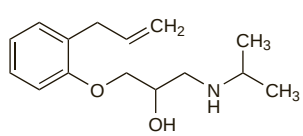
Proprietary Preparations (details are given in Part 3)
Cz.: Enviage; Rasilez; Riprazo; Sprimeo; Tekturna; ***Fr.:*** Rasilez; ***Port.:*** Enviage; Rasilez; Riprazo; Tekturna; ***UK:*** Rasilez; ***USA:*** Tekturna.

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-