7. Kingma K, *et al.* Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. *J Cardiovasc Pharmacol* 1995; **26:** 388–93.
8. Denton CP, Black CM. Raynaud's phenomenon and scleroderma. In: Snaith ML, ed. *ABC of rheumatology.* 3rd ed. London: BMJ Publishing Group, 2004: 87–91.

Pulmonary hypertension. Epoprostenol was originally introduced into the management of end-stage pulmonary hypertension (p.1179) to sustain patients long enough for them to have heart-lung transplantation. However, long-term therapy may also have a role as an alternative to transplantation; sustained clinical improvement and improved survival have been reported[1-4] in some patients with idiopathic pulmonary arterial hypertension given long-term intravenous therapy using portable infusion pumps, as well as in patients with pulmonary arterial hypertension associated with other diseases.[4-7]

Inhaled epoprostenol, a route that may overcome some of the adverse effects associated with parenteral use, has had some success in adults[8,9] with pulmonary hypertension and in neonates[10,11] with persistent pulmonary hypertension.

1. Higenbottam T, *et al.* Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; **80:** 151–5.
2. Herner SJ, Mauro LS. Epoprostenol in primary pulmonary hypertension. *Ann Pharmacother* 1999; **33:** 340–7.
3. McLaughlin VV, *et al.* Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; **106:** 1477–82.
4. Kuhn KP, *et al.* Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; **167:** 580–6.
5. McLaughlin VV, *et al.* Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999; **130:** 740–3.
6. Badesch DB, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 425–34.
7. Fisher KA, *et al.* Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest* 2006; **130:** 1481–8.
8. Olschewski H, *et al.* Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996; **124:** 820–4.
9. Mikhail G, *et al.* An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. *Eur Heart J* 1997; **18:** 1499–1504.
10. Bindl L, *et al.* Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994; **71:** F214–F216.
11. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.

Stroke. Results with epoprostenol in patients with acute stroke have been inconclusive and a systematic review of randomised studies concluded that too few patients had been studied for the effect of epoprostenol on survival to be determined.[1]

1. Bath PMW. Prostacyclin and analogues for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 04/07/05).

Thrombotic microangiopathies. Platelet aggregation has a major role in the pathogenesis of thrombotic thrombocytopenic purpura and the related disorder, haemolytic-uraemic syndrome (p.1076). Prostacyclin deficiency has been demonstrated in both conditions, but case reports of epoprostenol[1,2] or iloprost[3,4] treatment have indicated variable results.

1. Bobbio-Pallavicini E, *et al.* Intravenous prostacyclin (as epoprostenol) infusion in thrombotic thrombocytopenic purpura: four case reports and review of the literature. *Haematologica* 1994; **79:** 429–37.
2. Series C, *et al.* Interet de la prostacycline dans le traitement du syndrome hémolytique et urémique: à propos d'un cas. *Rev Med Interne* 1996; **17:** 76–8.
3. Sagripanti A, *et al.* Iloprost in the treatment of thrombotic microangiopathy: report of thirteen cases. *Biomed Pharmacother* 1996; **50:** 350–6.
4. Salvi F, *et al.* Unsuccessful treatment of resistant thrombotic thrombocytopenic purpura with prostacyclin. *Haematologica* 2000; **85:** 1329–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Flolan; ***Austria:*** Epoallen; Flolan; Glaxoprost; ***Belg.:*** Flolan; ***Canad.:*** Flolan; ***Cz.:*** Flolan; ***Denm.:*** Flolan; ***Fr.:*** Flolan; ***Gr.:*** Flolan; ***Irl.:*** Flolan; ***Israel:*** Flolan; ***Ital.:*** Flolan; ***Neth.:*** Flolan; ***Norw.:*** Flolan; ***Singapore:*** Flolan; ***Spain:*** Flolan; ***Switz.:*** Flolan; ***UK:*** Flolan; ***USA:*** Flolan.

Eprosartan Mesilate *(BANM, rINNM)*

Éprosartan, Mésilate d'; Eprosartan Mesylate *(USAN)*; Eprosartani Mesilas; Mesilato de eprosartán; SKF-108566-J. (*E*)-2-Butyl-1-(*p*-carboxybenzyl)-α-2-thenylimidazole-5-acrylic acid methanesulfonate.

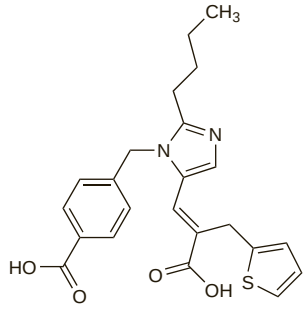
Эпрозартана Мезилат

$C_{23}H_{24}N_2O_4S,CH_4O_3S$ = 520.6.

CAS — 133040-01-4 (eprosartan); 144143-96-4 (eprosartan mesilate).

ATC — C09CA02.

ATC Vet — QC09CA02.



(eprosartan)

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Eprosartan is absorbed from the gastrointestinal tract with an absolute oral bioavailability of about 13%. Peak plasma concentrations occur about 1 to 2 hours after an oral dose in the fasted state; giving doses with food delays absorption but this is not clinically significant. Eprosartan is about 98% bound to plasma proteins. It is excreted in the bile and in the urine, primarily as the unchanged drug; after oral doses approximately 7% of the drug is excreted in the urine, with about 2% as the acyl glucuronide. The terminal elimination half-life is about 5 to 9 hours.

◊ References.

1. Martin DE, *et al.* Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. *J Clin Pharmacol* 1998; **38:** 129–37.
2. Tenero DM, *et al.* Effect of age and gender on the pharmacokinetics of eprosartan. *Br J Clin Pharmacol* 1998; **46:** 267–70.

Uses and Administration

Eprosartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171).

Eprosartan is given orally as the mesilate but doses are expressed in terms of the base; eprosartan mesilate 1.2 mg is equivalent to about 1 mg of eprosartan. The onset of antihypertensive effect occurs about 1 to 2 hours after administration and the maximum effect is achieved within 2 to 3 weeks after initiating therapy.

In the management of hypertension, eprosartan is given in an initial dose of 600 mg once daily. A lower initial dose of 300 mg once daily may be used in elderly patients over 75 years and has been recommended in renal or hepatic impairment (but see below). The dose should be adjusted according to response; the usual maintenance dose is 400 to 800 mg daily in a single dose or in two divided doses.

◊ Reviews.

1. McClellan KJ, Balfour JA. Eprosartan. *Drugs* 1998; **55:** 713–18.
2. Plosker GL, Foster RH. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2000; **60:** 177–201.
3. Robins GW, Scott LJ. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2005; **65:** 2355–77.
4. Ram CV, Rudmann MA. Unique dual mechanism of action of eprosartan: effects on systolic blood pressure, pulse pressure, risk of stroke and cognitive decline. *Expert Rev Cardiovasc Ther* 2007; **5:** 1003–11.

Administration in hepatic or renal impairment. In the UK a lower initial dose of 300 mg daily of eprosartan is recommended in patients with renal impairment (creatinine clearance less than 60 mL/minute) or mild to moderate hepatic impairment; this seems to be due to lack of clinical experience in such patients. In the USA, however, no reduction in the initial dose is considered necessary in hepatic or renal impairment, but a maximum dose of 600 mg daily is recommended for patients with moderate or severe renal impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Teveten; ***Austria:*** Teveten; ***Belg.:*** Teveten; ***Canad.:*** Teveten; ***Cz.:*** Teveten; ***Denm.:*** Teveten; ***Fin.:*** Teveten; ***Fr.:*** Teveten; ***Ger.:*** Emestar Mono; Teveten; ***Gr.:*** Epratenz†; Teveten; ***Hong Kong:*** Teveten; ***Hung.:*** Teveten; ***Irl.:*** Teveten; ***Ital.:*** Tevetenz; ***Neth.:*** Teveten; ***Norw.:*** Teveten; ***Philipp.:*** Teveten; ***Pol.:*** Teveten; ***Port.:*** Teveten; ***Rus.:*** Teveten (Теветен); ***S.Afr.:*** Teveten; ***Spain:*** Futuran; Navixen; Regulaten; Tevetens; ***Swed.:*** Teveten; ***Switz.:*** Teveten; ***Thai.:*** Teveten; ***UK:*** Teveten; ***USA:*** Teveten.

Multi-ingredient: ***Austral.:*** Teveten Plus; ***Austria:*** Teveten Plus; ***Belg.:*** Teveten Plus; ***Canad.:*** Teveten Plus; ***Cz.:*** Teveten Plus H; ***Denm.:*** Teveten Comp; ***Fin.:*** Teveten Comp; ***Fr.:*** Coteveten; ***Ger.:*** Emestar plus; Teveten Plus; ***Gr.:*** Teveten Plus; ***Hong Kong:*** Teveten Plus; ***Irl.:*** Teveten Plus; ***Neth.:*** Teveten Plus; ***Norw.:*** Teveten Comp; ***Philipp.:*** Teveten Plus; ***Port.:*** Medinor; Tensival; Teveten Plus; ***Rus.:*** Teveten Plus (Теветен Плюс); ***Spain:*** Futuran Plus; Navixen Plus; Regulaten Plus; Tevetens Plus; ***Swed.:*** Teveten Comp; ***Switz.:*** Teveten Plus; ***USA:*** Teveten HCT.

Eptifibatide *(BAN, rINN)*

C68-22; Eptifibatid; Eptifibatida; Eptifibatidi; Eptifibatidum; Integrelin; SB-1; Sch-60936. N^6-Amidino-N^2-(3-mercaptopropionyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide; S^1,S^6-Cyclo[N^6-carbamimidoyl-N^2-(3-sulfanylpropanoyl)-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide].

Эптифибатид

$C_{35}H_{49}N_{11}O_9S_2$ = 832.0.

CAS — 148031-34-9; 157630-07-4.

ATC — B01AC16.

ATC Vet — QB01AC16.

Adverse Effects

Bleeding is the most common adverse effect of eptifibatide. Hypotension has been reported. Antibodies to eptifibatide have not been detected.

Effects on the blood. Thrombocytopenia is an established adverse effect of the glycoprotein IIb/IIIa-receptor antagonist abciximab (see p.1192) but appears to be less common with eptifibatide. However, there have been several reports[1-5] of severe thrombocytopenia associated with eptifibatide.

1. Paradiso-Hardy FL, *et al.* Severe thrombocytopenia possibly related to readministration of eptifibatide. *Catheter Cardiovasc Interv* 2001; **54:** 63–7.
2. Hongo RH, Brent BN. Association of eptifibatide and acute profound thrombocytopenia. *Am J Cardiol* 2001; **88:** 428–31.
3. Yoder M, Edwards RF. Reversible thrombocytopenia associated with eptifibatide. *Ann Pharmacother* 2002; **36:** 628–30.
4. Coons JC, *et al.* Eptifibatide-associated acute, profound thrombocytopenia. *Ann Pharmacother* 2005; **39:** 368–72.
5. Refaat M, *et al.* Eptifibatide-induced thrombocytopenia. *J Thromb Thrombolysis* 2008; **25:** 204–6.

Precautions

As for Abciximab, p.1192.

Pharmacokinetics

Antiplatelet effects of eptifibatide persist for about 4 hours after stopping a continuous infusion. Plasma elimination half-life is about 2.5 hours. Eptifibatide is about 25% bound to plasma proteins. Renal clearance, as eptifibatide and metabolites excreted in the urine, accounts for about 50% of total body clearance.

Uses and Administration

Eptifibatide is an antiplatelet drug that reversibly inhibits its binding of fibrinogen, von Willebrand factor, and other adhesive molecules to the glycoprotein IIb/IIIa receptor of platelets. It is used, usually in combination with aspirin and heparin, in the management of unstable angina and in patients undergoing coronary angioplasty and stenting procedures.

In the management of **unstable angina**, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection, followed by 2 micrograms/kg per minute by intravenous infusion, for up to 72 hours. If percutaneous coronary intervention is performed during eptifibatide therapy, the infusion should be continued for 18 to 24 hours after the procedure, to a maximum total duration of 96 hours of therapy.

In patients undergoing **angioplasty**, though not presenting with unstable angina, eptifibatide is given in an initial dose of 180 micrograms/kg by intravenous injection immediately before the procedure, followed by 2 micrograms/kg per minute by intravenous infusion, with a second 180 micrograms/kg intravenous injection given 10 minutes after the first. The infusion should be continued until hospital discharge or for up to 18 to 24 hours; a minimum of 12 hours is recommended.