tion was 2.16 hours in a patient with hepatic impairment and 1.33 hours in a patient with renal impairment. The mean elimination half-life in patients with normal hepatic and renal function was 1.26 hours. It was suggested that patients with renal impairment should be monitored and have plasma concentrations measured during continuous infusions and that in hepatic disease the dosage may need to be modified.[1] Similarly, in a study[2] in paediatric patients receiving intravenous enoximone clearance was reduced in those with renal or hepatic impairment and it was suggested that the infusion rate should be decreased in such patients.

1. Desager JP, *et al.* Plasma enoximone concentrations in cardiac patients. *Curr Ther Res* 1990; **47:** 743–52.
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Beta blocker overdosage. Enoximone, given intravenously as a bolus dose of 0.5 mg/kg followed by an infusion of 15 micrograms/kg per minute, successfully increased the cardiac output and stroke volume in a woman who had ingested 10 g of metoprolol.[1] It was suggested that enoximone may be useful in such patients since its action does not involve the beta-adrenergic system. Use to treat propranolol overdose has also been described.[2]

1. Hoeper MM, Boeker KHW. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335:** 1538.
2. Sandroni C, *et al.* Enoximone in cardiac arrest caused by propranolol: two case reports. *Acta Anaesthesiol Scand* 2006; **50:** 759–61.

Heart failure. Enoximone is one of several drugs that may be used in heart failure (p.1165), but because of an increased mortality rate reported following long-term oral use it is only given intravenously for short-term management of heart failure unresponsive to other treatments. In a comparison of oral enoximone and placebo in patients with moderate to moderately severe heart failure,[1] enoximone was no better than placebo in improving exercise duration over the 16-week study period. Although the overall incidence of adverse effects was similar in the two groups, 5 patients receiving enoximone died compared with none in the placebo group. Low doses of oral enoximone (generally 25 or 50 mg three times daily) have been tried in an attempt to wean patients with severe (NYHA class IV) heart failure from intravenous inotropic support, but with little or only limited success.[2]

1. Uretsky BF, *et al.* Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. *Circulation* 1990; **82:** 774–80.
2. Feldman AM, *et al.* EMOTE Study Group. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; **154:** 861–9.

Preparations

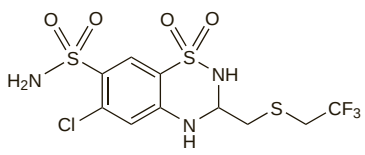
Proprietary Preparations (details are given in Part 3)
Belg.: Perfan; ***Fr.:*** Perfane†; ***Ger.:*** Perfan; ***Irl.:*** Perfan; ***Ital.:*** Perfan; ***Neth.:*** Perfan; ***UK:*** Perfan.

Epitizide *(BAN, rINN)* ⊗

Epithiazide *(USAN)*; Epitizida; Épitizide; Epitizidum; Eptizida; NSC-108164; P-2105. 6-Chloro-3,4-dihydro-3-(2,2,2-trifluoroethylthiomethyl)-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Эпитизид

$C_{10}H_{11}ClF_3N_3O_4S_3$ = 425.9.
CAS — 1764-85-8.



Profile

Epitizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) used in the treatment of hypertension and oedema, often with triamterene.

Preparations

Proprietary Preparations (details are given in Part 3)

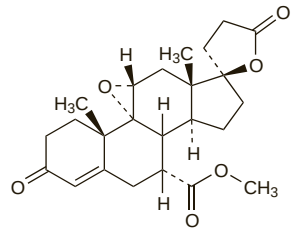
Multi-ingredient: ***Belg.:*** Dyta-Urese; ***Neth.:*** Dyta-Urese.

Eplerenone *(USAN, rINN)* ⊗

Eplerenona; Éplérénone; Eplerenonum; SC-66110. 9,11α-Epoxy-17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone methyl ester.

Эплеренон

$C_{24}H_{30}O_6$ = 414.5.
CAS — 107724-20-9.
ATC — C03DA04.
ATC Vet — QC03DA04.



Adverse Effects

As for Spironolactone, p.1400. Hypercholesterolaemia, hypertriglyceridaemia, and increases in liver enzymes have also occurred.

Precautions

As for Spironolactone, p.1400.

Interactions

As for Spironolactone, p.1401.

Eplerenone is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and significantly increased plasma concentrations of eplerenone have occurred when potent inhibitors of this enzyme have been given. These include clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, and ritonavir, and use with eplerenone is contra-indicated. Mild to moderate inhibitors of this enzyme, such as erythromycin, fluconazole, saquinavir, and verapamil, have a less marked effect, although a reduced dose of eplerenone may be necessary (see under Uses, below). Grapefruit juice causes only a small increase in exposure to eplerenone. Conversely, inducers of this enzyme system, such as carbamazepine, St John's wort, phenobarbital, phenytoin, and rifampicin, may reduce plasma concentrations of eplerenone.

Pharmacokinetics

Peak plasma concentrations of eplerenone are reached about 1.5 hours after an oral dose; they are dose proportional for doses of 25 to 100 mg, and less than proportional above 100 mg. Protein binding, primarily to α_1-acid glycoprotein, is about 50%. Eplerenone metabolism is mainly mediated by the cytochrome P450 isoenzyme CYP3A4; less than 5% of a dose is excreted unchanged. About 32% of a dose is excreted in the faeces, and the remainder in the urine. The elimination half-life is about 4 to 6 hours. Eplerenone is not removed by dialysis.

◊ References.

1. Ravis WR, *et al.* Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *J Clin Pharmacol* 2005; **45:** 810–21.

Uses and Administration

Eplerenone is an aldosterone antagonist with properties similar to those of spironolactone (p.1401) but with a higher selectivity for the aldosterone receptor. It is given orally in the management of hypertension (p.1171) and heart failure (p.1165).

In the management of **hypertension**, eplerenone may be given alone or with other antihypertensives. It is given in an initial dose of 50 mg daily, increasing if necessary to a maximum of 50 mg twice daily. While eplerenone should not be given with potent CYP3A4 inhibitors (see Interactions, above), patients taking mild to moderate inhibitors may be given eplerenone; the initial dose should be reduced to 25 mg daily.

For the management of **heart failure** after myocardial infarction, eplerenone is given in an initial dose of 25 mg daily, increasing to 50 mg daily within 4 weeks if tolerated. Eplerenone should be withdrawn or the dose should be reduced to 25 mg daily, or on alternate days, if hyperkalaemia develops. Eplerenone may be used in patients given mild to moderate CYP3A4 inhibitors, at a dose not exceeding 25 mg daily.

◊ References and reviews.

1. Zillich AJ, Carter BL. Eplerenone—a novel selective aldosterone blocker. *Ann Pharmacother* 2002; **36:** 1567–76.
2. Pitt B, *et al*, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309–21. Correction. *ibid.*; 2271.
3. Keating GM, Plosker GL. Eplerenone: a review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004; **64:** 2689–707.
4. Pitt B, *et al.* Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; **46:** 425–31.
5. Anonymous. Eplerenone after myocardial infarction? *Drug Ther Bull* 2008; **46:** 1–3.

Preparations

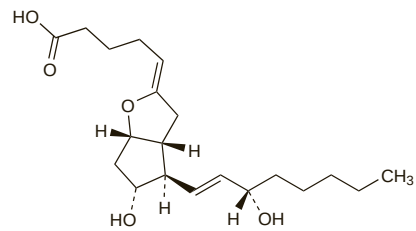
Proprietary Preparations (details are given in Part 3)
Austral.: Inspra; ***Austria:*** Inspra; ***Chile:*** Inspra; ***Cz.:*** Inspra; ***Denm.:*** Inspra; ***Fin.:*** Inspra; ***Fr.:*** Inspra; ***Ger.:*** Inspra; ***Hong Kong:*** Inspra; ***Hung.:*** Inspra; ***Irl.:*** Inspra; ***Mex.:*** Inspra; ***Neth.:*** Inspra; ***Norw.:*** Inspra; ***Port.:*** Inovic; Inspra; ***Spain:*** Elecor; Inspra; ***Swed.:*** Inspra; ***UK:*** Inspra; ***USA:*** Inspra.

Epoprostenol *(USAN, rINN)*

Époprosténol; Epoprostenoli; Epoprostenolum; PGI_2; PGX; Prostacyclin; Prostacyclinum; Prostacyklin; Prostaglandin I_2; Prostaglandin X; Prostasykliini; U-53217. (5*Z*,13*E*)-(8*R*,9*S*,11*R*,12*R*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-5,13-dienoic acid; (*Z*)-5-{(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]perhydrocyclopenta[*b*]furan-2-ylidene}valeric acid.

Эпопростенол

$C_{20}H_{32}O_5$ = 352.5.
CAS — 35121-78-9.
ATC — B01AC09.
ATC Vet — QB01AC09.



NOTE. In *Martindale* the term epoprostenol is used for the exogenous substance and prostacyclin for the endogenous substance.

Epoprostenol Sodium *(BAN, USAN, rINNM)*

Epoprostenol sódico; Époprosténol Sodique; Natrii Epoprostenolum; U-53217A.

Натрий Эпопростенол

$C_{20}H_{31}NaO_5$ = 374.4.
CAS — 61849-14-7.
ATC — B01AC09.
ATC Vet — QB01AC09.

Stability in solution. Epoprostenol is unstable at physiological pH and solutions for infusion are prepared in an alkaline glycine buffer at pH 10.5. The half-life in aqueous solution of pH 7.4 has been reported[1] to be less than 3 minutes at 37°, but increased stability has been reported in plasma, albumin, or whole blood.[1,2]

1. El Tahir KEH, *et al.* Stability of prostacyclin in human plasma. *Clin Sci* 1980; **59:** 28P–29P.
2. Mikhailidis DP, *et al.* Infusion of prostacyclin (epoprostenol). *Lancet* 1982; **ii:** 767.

Adverse Effects and Precautions

The incidence of adverse reactions to epoprostenol is dose-related. Adverse effects during intravenous infusion commonly include hypotension, increased heart rate, flushing, and headache. Dosage should be reduced or the epoprostenol infusion stopped if excessive hypotension occurs. Bradycardia with pallor, sweating, nausea, and abdominal discomfort may occur. Erythema over the intravenous infusion site has been noted. Other adverse effects reported have includ-

ed nausea and vomiting, diarrhoea, jaw pain or non-specific musculoskeletal pain, anxiety, nervousness, tremor, flu-like symptoms, hyperglycaemia, drowsiness, and chest pain.

Coagulation of blood in the dialysis circuit has been reported rarely in patients given epoprostenol but no conventional anticoagulant. The use of epoprostenol for pulmonary hypertension is contra-indicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction, and in patients who develop pulmonary oedema during dose-ranging. Sudden withdrawal of epoprostenol should be avoided because of the risk of rebound pulmonary hypertension. Haematological and cardiovascular monitoring is required in patients receiving epoprostenol infusions. Care should be taken to avoid extravasation.

Incidence of adverse effects. A study in 24 healthy subjects investigated the incidence of adverse effects with intravenous infusions of epoprostenol of up to 10 nanograms/kg per minute for up to 100 minutes.[1] Subjects varied in their susceptibility to epoprostenol but the same sequence of events was usually present. A change in pre-ejection period and facial flushing was often apparent at an infusion rate of 2 to 2.5 nanograms/kg per minute. A rise in heart rate and change in other cardiovascular variables was present when the infusion rate had increased to 4 to 5 nanograms/kg per minute; headache, generally the dose-limiting factor, was usually present at this dose and increased as the dose was raised, as did the other effects. Erythema over the vein and 'vagal reflex' only appeared after at least 1 hour of infusion; 'vagal reflex' took only a few seconds to develop.

Early studies showing that high doses were well tolerated had been conducted using a form of epoprostenol probably only half as potent as the commercially available product. It was proposed that 4 nanograms/kg per minute should in general be the maximum infusion rate for prolonged infusions, although higher rates could be tolerated in anaesthetised patients. Careful attention to infusion technique is necessary and monitoring of the heart rate is advisable in view of the suddenness with which the 'vagal reflex' can occur. Most of the adverse effects reported here have responded to a reduction in dosage.

1. Pickles H, O'Grady J. Side effects occurring during administration of epoprostenol (prostacyclin, PGI), in man. *Br J Clin Pharmacol* 1982; **14:** 177–85.

Effects on the blood. Reports of rebound platelet activation during continuous epoprostenol infusion.[1,2]

1. Yardumian DA, Machin SJ. Altered platelet function in patients on continuous infusion of epoprostenol. *Lancet* 1984; **i:** 1357.
2. Sinzinger H, *et al.* Rebound platelet activation during continuous epoprostenol infusion. *Lancet* 1984; **ii:** 759.

Effects on the cardiovascular system. Evidence that epoprostenol and its analogue iloprost can induce myocardial ischaemia in patients with coronary artery disease.[1]

1. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.

Effects on mental state. Symptoms of depression were associated with intravenous epoprostenol therapy in 4 patients.[1]

1. Ansell D, *et al.* Depression and prostacyclin infusion. *Lancet* 1986; **ii:** 509.

Hypersensitivity. Severe erythroderma occurred in a woman with undifferentiated connective tissue disease who was treated with epoprostenol for pulmonary hypertension.[1] Diffuse erythema, pruritus, and scaling, with chills, nausea, vomiting, and diarrhoea, developed about 2 months after starting therapy, and resolved with epoprostenol withdrawal and corticosteroid treatment.

1. Ahearn GS, *et al.* Severe erythroderma as a complication of continuous epoprostenol therapy. *Chest* 2002; **122:** 378–80.

Interactions

Since epoprostenol is a potent vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants. Epoprostenol may slightly increase serum concentrations of digoxin, and may reduce the thrombolytic effect of alteplase by increasing its hepatic clearance. The hypotensive effects of epoprostenol may be exacerbated by using acetate in dialysis fluids.

Anticoagulants. The incidence of bleeding complications was examined in a retrospective review[1] of 31 patients with primary pulmonary hypertension who had been treated with continuous intravenous epoprostenol and oral *warfarin*. Nine patients developed 11 bleeding episodes, including 9 episodes of alveolar haemorrhage. The international normalised ratio (INR) was maintained in the therapeutic range for 8 of these patients, suggesting that the effect was not caused by overdose of warfarin. The risk of bleeding appeared to be increased in patients who received high-dose epoprostenol (mean dose 89 nanograms/kg per minute).

1. Ogawa A, *et al.* Risk of alveolar hemorrhage in patients with primary pulmonary hypertension—anticoagulation and epoprostenol therapy. *Circ J* 2005; **69:** 216–20.

Pharmacokinetics

Endogenous prostacyclin is a product of arachidonic acid metabolism with a very short half-life. On intravenous infusion epoprostenol is hydrolysed rapidly to the more stable but much less active 6-keto-prostaglandin $F_{1\alpha}$ (6-oxo-prostaglandin $F_{1\alpha}$). A second metabolite, 6,15-diketo-13,14-dihydro-prostaglandin $F_{1\alpha}$, is formed by enzymatic degradation. Unlike many other prostaglandins, epoprostenol is not inactivated in the pulmonary circulation.

Uses and Administration

Epoprostenol is a prostaglandin (p.2374) that causes vasodilatation and prevents platelet aggregation. The endogenous substance is termed prostacyclin. Epoprostenol is used mainly in extracorporeal procedures and in pulmonary hypertension.

Epoprostenol is given as the sodium salt and doses are expressed in terms of the base; 1.06 nanograms of epoprostenol sodium is equivalent to about 1 nanogram of epoprostenol. The drug is unstable in solution at physiological pH and also has a very short duration of action because of its rapid hydrolysis *in vivo*. It must therefore be given by continuous infusion. Great care must be taken in preparing a suitably diluted solution for infusion and only diluent as supplied by the manufacturer should be used to reconstitute epoprostenol.

Epoprostenol is used to **prevent platelet aggregation** when blood is brought into contact with nonbiological surfaces in procedures such as extracorporeal circulation, especially in renal dialysis patients. It is indicated for use when heparin carries a high risk of causing or exacerbating bleeding, or is otherwise contra-indicated. Epoprostenol is given by continuous intravenous infusion or into the blood supplying the extracorporeal circulation. The usual dose for renal dialysis is 4 nanograms/kg per minute intravenously before dialysis, then 4 nanograms/kg per minute into the arterial inlet of the dialyser during dialysis.

In the long-term treatment of primary **pulmonary hypertension** or pulmonary hypertension associated with scleroderma a dose-ranging procedure is performed first. Epoprostenol infusion is started at a rate of 2 nanograms/kg per minute, then increased by increments of 2 nanograms/kg per minute at intervals of at least 15 minutes until the maximum haemodynamic benefit or dose-limiting effects occur. Epoprostenol is then given by continuous infusion through a central venous catheter, the initial rate being 4 nanograms/kg per minute *less than* the maximum-tolerated infusion rate; if the maximum-tolerated infusion rate is less than 5 nanograms/kg per minute, then the initial rate should be one-half of this maximum rate. The maintenance dose is subsequently adjusted according to the patient's response. If symptoms recur or if adverse effects occur the dosage may be increased or decreased by steps of 1 to 2 nanograms/kg per minute at intervals of at least 15 minutes until a new maintenance dose is established.

For the use of epoprostenol in neonates and children, see below.

Action. The discovery, properties, and clinical applications of prostacyclin have been reviewed.[1] Prostacyclin is the main product of arachidonic acid in vascular tissues, endothelial cells from vessel walls being the most active producers. It is a strong hypotensive agent through vasodilatation of vascular beds, including the pulmonary and cerebral circulations, and is also a potent endogenous inhibitor of platelet aggregation. Inhibition of aggregation is achieved by stimulation of adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP) levels in the platelets. By inhibiting several steps in the activation of the arachidonic acid metabolic cascade, prostacyclin exerts an overall control of platelet aggregability.

Endogenous prostacyclin and thromboxane A_2 may be of more physiological and pathological importance[2] than the more classical prostanoids prostaglandin E_2 and prostaglandin F_2 . They have directly opposing pharmacological actions in many systems, such as on platelet function, vascular smooth muscle, bronchopulmonary function, and gastrointestinal integrity. Thus prostanoid-mediated control of cellular and tissue function may reflect an interactive modulation between prostacyclin and thromboxane A_2 with imbalance resulting in dysfunction, for example in platelet and vascular disorders. Thromboxane A_2 has both bronchoconstrictor and pulmonary irritant actions and has brought about marked changes in respiratory function in experimental models; prostacyclin may oppose these effects on both the pulmonary vasculature and bronchial smooth muscle. Thromboxane A_2 has induced marked renal vasoconstriction *in vitro* whereas renal vasodilatation and stimulation of the release of renin has followed the administration of epoprostenol [exogenous prostacyclin] in *animals*. In contrast to the pro-ulcerogenic actions of thromboxane A_2, epoprostenol and its analogues, like other prostaglandins, have potent gastrointestinal anti-ulcer properties which can be disassociated from their gastric antisecretory properties. The term 'cytoprotection' has been used to describe this ability of exogenous prostaglandins to prevent gastrointestinal damage; endogenous prostaglandins might have a similar protective role. Epoprostenol also has a cytoprotective effect against experimental damage in the gastric mucosa, myocardium, and liver whereas thromboxane A_2 has a cytolytic effect.

1. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995; **75:** 3A–10A.
2. Whittle BJR, Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull* 1983; **39:** 232–8.

Acute respiratory distress syndrome. Encouraging results[1-3] have been seen with inhaled epoprostenol in the treatment of acute respiratory distress syndrome (p.1498).

1. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; **342:** 961–2.
2. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153:** 991–6.
3. van Heerden PV, *et al.* Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000; **117:** 819–27.

Administration in children. Although epoprostenol is not licensed for the treatment of children, it has been used successfully in children with primary pulmonary hypertension[1,2] and in neonates with persistent pulmonary hypertension of the newborn.[3] It is usually given by continuous intravenous infusion, but in neonates the inhaled[4] and endotracheal[5] routes have also been used.

For children aged 1 month to 18 years with *primary pulmonary hypertension*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, increasing as necessary to 40 nanograms/kg per minute. Children on prolonged treatment can become tolerant to epoprostenol and higher doses have been used.[1,2]

For neonates with *persistent pulmonary hypertension of the newborn*, the *BNFC* suggests that epoprostenol may be given by continuous intravenous infusion in an initial dose of 2 nanograms/kg per minute, adjusted according to response up to a usual maximum of 20 nanograms/kg per minute (rarely up to 40 nanograms/kg per minute).

1. Barst RJ, *et al.* Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999; **99:** 1197–1208.
2. Lammers AE, *et al.* Epoprostenol treatment in children with severe pulmonary hypertension. *Heart* 2007; **93:** 739–43.
3. Eronen M, *et al.* Prostacyclin treatment for persistent pulmonary hypertension of the newborn. *Pediatr Cardiol* 1997; **18:** 3–7.
4. Kelly LK, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002; **141:** 830–2.
5. De Jaegere APMC, van den Anker JN. Endotracheal instillation of prostacyclin in preterm infants with persistent pulmonary hypertension. *Eur Respir J* 1998; **12:** 932–4.

Heart failure. Epoprostenol has been investigated for the treatment of heart failure but development was abandoned due to an increase in mortality associated with long-term use.[1,2]

1. Phillips BB, Gandhi AJ. Epoprostenol in the treatment of congestive heart failure. *Am J Health-Syst Pharm* 1997; **54:** 2613–15.
2. Califf RM, *et al.* A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997; **134:** 44–54.

Peripheral vascular disease. Various prostaglandins including epoprostenol have been used for their vasodilating effect in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy.

References.

1. Szczeklik A, *et al.* Successful therapy of advanced arteriosclerosis obliterans with prostacyclin. *Lancet* 1979; **i:** 1111–14.
2. Belch JJF, *et al.* Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome: a double-blind controlled trial. *Lancet* 1983; **i:** 313–15.
3. Belch JJF, *et al.* Epoprostenol (prostacyclin) and severe arterial disease: a double-blind trial. *Lancet* 1983; **i:** 315–17.
4. De San Lazaro C, *et al.* Prostacyclin in severe peripheral vascular disease. *Arch Dis Child* 1985; **60:** 370–84.
5. Leaker B, *et al.* Treatment of acute renal failure, symmetrical peripheral gangrene, and septicaemia with plasma exchange and epoprostenol. *Lancet* 1987; **i:** 156.
6. Negus D, *et al.* Intra-arterial prostacyclin compared to Praxilene in the management of severe lower limb ischaemia: a double-blind trial. *J Cardiovasc Surg* 1987; **28:** 196–9.

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.

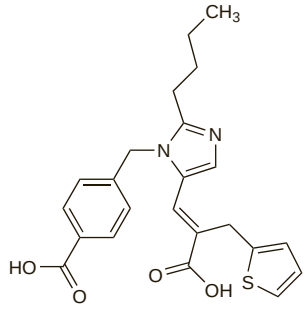
Эпрозартана Мезилат

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