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

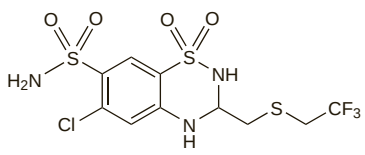
Proprietary Preparations (details are given in Part 3)
Belg.: Perfan; ***Fr.:*** Perfane†; ***Ger.:*** Perfan; ***Irl.:*** Perfan; ***Ital.:*** Perfan; ***Neth.:*** Perfan; ***UK:*** Perfan.

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)

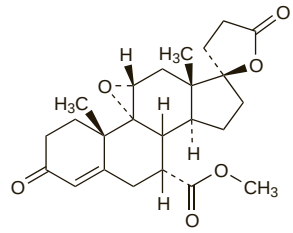
Multi-ingredient: ***Belg.:*** Dyta-Urese; ***Neth.:*** Dyta-Urese.

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

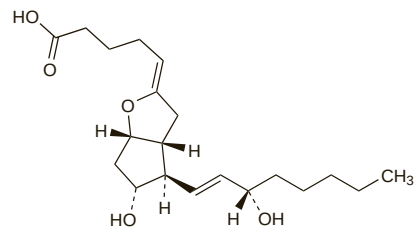
Proprietary Preparations (details are given in Part 3)
Austral.: Inspra; ***Austria:*** Inspra; ***Chile:*** Inspra; ***Cz.:*** Inspra; ***Denm.:*** Inspra; ***Fin.:*** Inspra; ***Fr.:*** Inspra; ***Ger.:*** Inspra; ***Hong Kong:*** Inspra; ***Hung.:*** Inspra; ***Irl.:*** Inspra; ***Mex.:*** Inspra; ***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-