hours after operation. After hip replacement surgery, enoxaparin sodium may be continued in a dose of 40 mg (4000 units) once daily for a further 3 weeks.

- For the prophylaxis of thromboembolism in immobilised medical patients, the dose is 40 mg (4000 units) once daily for at least 6 days; treatment should be continued until the patient is fully ambulant, up to a maximum of 14 days.

For the *treatment* of deep-vein thrombosis enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours, or 1.5 mg/kg (150 units/kg) once daily, for at least 5 days and until oral anticoagulation is established.

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, enoxaparin sodium 1 mg/kg (100 units/kg) is introduced into the arterial line of the circuit at the beginning of the dialysis session. A further dose of 0.5 to 1 mg/kg (50 to 100 units/kg) may be given if required. The dose should be reduced in patients at high risk of haemorrhage.

In the management of **unstable angina**, enoxaparin sodium is given subcutaneously in a dose of 1 mg/kg (100 units/kg) every 12 hours. Treatment is usually continued for 2 to 8 days.

In acute ST-elevation **myocardial infarction** the initial dose of enoxaparin is 30 mg (3000 units) intravenously, with a subcutaneous dose of 1 mg/kg (100 units/kg) given at the same time. Further doses of 1 mg/kg (100 units/kg) should be given subcutaneously every 12 hours for 8 days or until hospital discharge. The first 2 subcutaneous doses should not exceed 100 mg (10 000 units) each. For patients who undergo a percutaneous coronary intervention, an additional intravenous dose of 300 micrograms/kg (30 units/kg) should be given at the time of the procedure if the last subcutaneous dose was given more than 8 hours previously. Patients aged 75 years and older with acute myocardial infarction should be given subcutaneous doses only; the recommended dose is 750 micrograms/kg (75 units/kg) every 12 hours, with a maximum of 75 mg (7500 units) for each of the first 2 doses.

The dose of enoxaparin sodium should be reduced in patients with severe renal impairment (see below).

◊ References.

1. Noble S, *et al.* Enoxaparin: a reappraisal of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disease. *Drugs* 1995; **49:** 388–410.
2. Noble S, Spencer CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. *Drugs* 1998; **56:** 259–72.
3. Harvey DM, Offord RH. Management of venous and cardiovascular thrombosis: enoxaparin. *Hosp Med* 2000; **61:** 628–36.
4. Ibbotson T, Goa KL. Enoxaparin: an update of its clinical use in the management of acute coronary syndromes. *Drugs* 2002; **62:** 1407–31.
5. Fareed J, *et al.* Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. *Clin Pharmacokinet* 2003; **42:** 1043–57.
6. Siddiqui MAA, Wagstaff AJ. Enoxaparin: a review of its use as thromboprophylaxis in acutely ill, nonsurgical patients. *Drugs* 2005; **65:** 1025–36.
7. Carter NJ, *et al.* Enoxaparin: a review of its use in ST-segment elevation myocardial infarction. *Drugs* 2008; **68:** 691–710.

Administration in infants and children. Increasing numbers of infants and children are given anticoagulants for the management of thromboembolism. Few controlled studies have been carried out in this age group and recommendations for therapy have generally been adapted from adult guidelines. Low-molecular-weight heparins may have a number of advantages in children. Enoxaparin has been used for the prophylaxis[1] of thromboembolism in children including neonates, and for treatment in children including neonates[1-3] and preterm infants.[1,3-5] Younger children may require a higher dose than older children. US guidelines recommend the following doses for *treatment*[6] of thromboembolism:

- under 2 months of age: 1.5 mg/kg (150 units/kg) every 12 hours
- over 2 months of age: 1 mg/kg (100 units/kg) every 12 hours

Doses for *prophylaxis*[6] are:

- under 2 months of age: 750 micrograms/kg (75 units/kg) every 12 hours
- over 2 months of age: 500 micrograms/kg (50 units/kg) every 12 hours

Similar doses are recommended in the UK by the *BNFC*, although it specifies slightly modified doses in neonates, in whom it recommends 1.5 to 2 mg/kg twice daily for *treatment* and 750 micrograms/kg twice daily for *prophylaxis*.

1. Dix D, *et al.* The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000; **136:** 439–45.
2. Massicotte P, *et al.* Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr* 1996; **128:** 313–18.
3. Streif W, *et al.* Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F365–F370.
4. Dunaway KK, *et al.* Use of enoxaparin in a preterm infant. *Ann Pharmacother* 2000; **34:** 1410–13.
5. Michaels LA, *et al.* Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. *Pediatrics* 2004; **114:** 703–7.
6. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 887S–968S.

Administration in renal impairment. Careful monitoring is required when enoxaparin sodium is given to patients with mild to moderate renal impairment.[1] In severe renal impairment (creatinine clearance less than 30 mL/minute) the dose should be reduced. For prophylaxis of venous thromboembolism, UK licensed product information recommends a dose of 20 mg (2000 units) subcutaneously once daily whereas US licensed product information recommends a subcutaneous dose of 30 mg (3000 units) once daily. For treatment of venous thromboembolism, unstable angina, or acute myocardial infarction in patients aged 75 years or older, a dose of 1 mg/kg (100 units/kg) subcutaneously once daily is advised; patients under 75 years with myocardial infarction should additionally be given a single intravenous dose of 30 mg (3000 units) with the first subcutaneous dose. However, the adequacy of a once-daily dose in patients with acute coronary syndromes has been questioned and alternative dosage regimens have been suggested.2,3

1. Brophy DF, Sica DA. Use of enoxaparin in patients with chronic kidney disease: safety considerations. *Drug Safety* 2007; **30:** 991–4.
2. Hulot J-S, *et al.* Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther* 2005; **77:** 542–52.
3. Green B, *et al.* Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 2005; **59:** 281–90.

Preparations

USP 31: Enoxaparin Sodium Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Clexane; Dilutol; ***Austral.:*** Clexane; ***Austria:*** Lovenox; ***Belg.:*** Clexane; ***Braz.:*** Clexane; Cutenox†; Dripanina; ***Canad.:*** Lovenox; ***Chile:*** Clexane; Nu-Rox; ***Cz.:*** Clexane; ***Denm.:*** Klexane; ***Fin.:*** Klexane; ***Fr.:*** Lovenox; ***Ger.:*** Clexane; ***Gr.:*** Clexane; ***Hong Kong:*** Clexane; ***Hung.:*** Clexane; ***India:*** Clexane; ***Indon.:*** Lovenox; ***Irl.:*** Clexane; ***Israel:*** Clexane; ***Ital.:*** Clexane; ***Malaysia:*** Clexane; ***Mex.:*** Clexane; ***Neth.:*** Clexane; ***Norw.:*** Klexane; ***NZ:*** Clexane; ***Philipp.:*** Clexane; ***Pol.:*** Clexane; ***Port.:*** Klexane; Lovenox; ***Rus.:*** Clexane (Клексан); ***S.Afr.:*** Clexane; ***Singapore:*** Clexane; ***Spain:*** Clexane; Decipar; ***Swed.:*** Klexane; ***Switz.:*** Clexane; ***Thai.:*** Clexane; ***Turk.:*** Clexane; ***UK:*** Clexane; ***USA:*** Lovenox; ***Venez.:*** Clexane; Enoparin.

Multi-ingredient: ***Cz.:*** Clexane anti Xa-IU.

Enoximone *(BAN, USAN, rINN)*

Enoksimoni; Enoximon; Enoximona; Énoximone; Enoximonum; Fenoximone; MDL-17043; MDL-19438; RMI-17043; YMDL-17043. 4-Methyl-5-[4-(methylthio)benzoyl]-4-imidazolin-2-one.

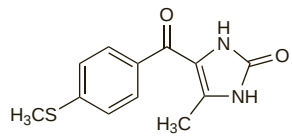
Эноксимон

$C_{12}H_{12}N_2O_2S$ = 248.3.

CAS — 77671-31-9.

ATC — C01CE03.

ATC Vet — QC01CE03.



Incompatibility. Crystal formation has occurred when enoximone injection was mixed in glass containers or syringes; the manufacturer recommends that only plastic containers or syringes are used for dilutions. The manufacturer also recommends that only sodium chloride 0.9% or water be used as diluents. Glucose solutions should not be used for dilution as crystal formation may occur.

Adverse Effects

Long-term oral treatment with enoximone has been reported to increase the mortality rate and enoximone is now only given intravenously for short-term use.

Enoximone may cause ventricular and supraventricular tachyarrhythmias, ectopic beats, and hypotension.

Adverse effects of enoximone affecting the gastrointestinal tract include diarrhoea, nausea, and vomiting. Other adverse effects include headache, insomnia, chills, oliguria, fever, urinary retention, and limb pain. There have been reports of thrombocytopenia and abnormal liver enzyme values.

Effects on the nervous system. Tonic-clonic convulsions have been reported[1] in a patient given enoximone 6 micrograms/kg per minute by intravenous infusion. The convulsions subsided when enoximone was stopped.

1. Appadurai I, *et al.* Convulsions induced by enoximone administered as a continuous intravenous infusion. *BMJ* 1990; **300:** 613–14.

Hyperosmolality. Hyperosmolality occurred in an infant during intravenous infusion of enoximone 20 micrograms/kg per minute. The probable cause was propylene glycol in the enoximone injection providing a dose of 2.4 mg/kg per minute.[1]

1. Huggon I, *et al.* Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990; **301:** 19–20.

Precautions

Enoximone should be used with caution in patients with hypertrophic cardiomyopathy or severe obstructive aortic or pulmonary valvular disease.

Blood pressure, heart rate, ECG, fluid and electrolyte status, and renal function should be monitored during therapy. Platelet count and liver enzyme values should also be monitored.

The injection has a high pH (about 12) and must be diluted before use (but see Incompatibility, above). Extravasation should be avoided.

Doses may need to be reduced in hepatic or renal impairment (see under Uses and Administration, below).

Pharmacokinetics

Although enoximone is absorbed from the gastrointestinal tract it is no longer given orally. The plasma elimination half-life varies widely; it may be about 1 to 4 hours in healthy subjects and about 3 to 8 hours in patients with heart failure, but longer times have been reported. Enoximone is about 85% bound to plasma proteins. It is metabolised in the liver and is excreted in the urine, mainly as metabolites. After intravenous doses about 70% of a dose is excreted in the urine as metabolites and less than 1% as unchanged drug.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).
2. Booker PD, *et al.* Enoximone pharmacokinetics in infants. *Br J Anaesth* 2000; **85:** 205–10.

Uses and Administration

Enoximone is a phosphodiesterase inhibitor similar to amrinone (p.1215) with positive inotropic and vasodilator activity. It is given intravenously in the short-term management of heart failure. In some long-term studies it was given orally, but an increased mortality rate was reported.

The usual initial dose of enoximone by intravenous injection is 0.5 to 1.0 mg/kg given at a rate not greater than 12.5 mg/minute. This may be followed by doses of 500 micrograms/kg every 30 minutes until a satisfactory response is obtained or a total dose of 3 mg/kg has been given. Alternatively, the initial dose may be given as a continuous intravenous infusion in a dose of 90 micrograms/kg per minute over 10 to 30 minutes until the desired response is achieved.

For maintenance therapy the initial dose (up to a total of 3 mg/kg) may be repeated as required every 3 to 6 hours or a continuous or intermittent infusion may be given in a dose of 5 to 20 micrograms/kg per minute.

The total dose over 24 hours should not exceed 24 mg/kg.

Dosage may need to be reduced in patients with hepatic or renal impairment (see below).

◊ General references.

1. Vernon MW, *et al.* Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991; **42:** 997–1017.

Administration in hepatic and renal impairment. The elimination half-life of enoximone after intravenous administra-

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

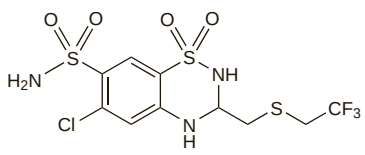
Proprietary Preparations (details are given in Part 3)
Belg.: Perfan; ***Fr.:*** Perfane†; ***Ger.:*** Perfan; ***Irl.:*** Perfan; ***Ital.:*** Perfan; ***Neth.:*** Perfan; ***UK:*** Perfan.

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)

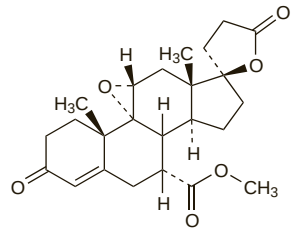
Multi-ingredient: ***Belg.:*** Dyta-Urese; ***Neth.:*** Dyta-Urese.

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

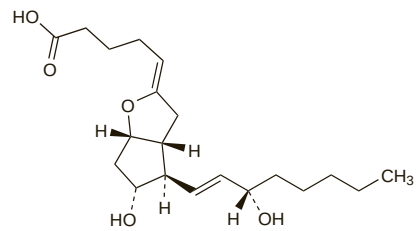
Proprietary Preparations (details are given in Part 3)
Austral.: Inspra; ***Austria:*** Inspra; ***Chile:*** Inspra; ***Cz.:*** Inspra; ***Denm.:*** Inspra; ***Fin.:*** Inspra; ***Fr.:*** Inspra; ***Ger.:*** Inspra; ***Hong Kong:*** Inspra; ***Hung.:*** Inspra; ***Irl.:*** Inspra; ***Mex.:*** Inspra;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