The dose of eptifibatide may need to be reduced in patients with renal impairment (see below).

♦ General references.

- 1. Gilchrist IC. Platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention: focus on the pharmacokinetic-pharmacodynamic relationships of eptifibatide. Clin Pharmacokinet 2003: 42: 703-20.
- 2. Curran MP, Keating GM. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. *Drugs* 2005; **65**: 2009–35.
- 3. Tricoci P, et al. Present and evolving role of eptifibatide in the treatment of acute coronary syndromes. Expert Rev Cardiovasc Ther 2007; 5: 401–12.
- 4. Zeymer U. The role of eptifibatide in patients undergoing percutaneous coronary intervention. Expert Opin Pharmacother 2007; 8: 1147-54.
- Zeymer U, Wienbergen H. A review of clinical trials with eptifi-batide in cardiology. Cardiovasc Drug Rev 2007; 25: 301–15.

Administration in renal impairment. The clearance of eptifibatide is reduced in renal impairment and plasma-eptifibatide concentrations are about doubled in patients with a creatinine clearance (CC) below 50 mL/minute. Eptifibatide should not be used in severe renal impairment; it is contra-indicated in patients with CC below 30 mL/minute in the UK, and in dialysis-dependent patients in the USA. In patients with moderate renal impairment (CC below 50 mL/minute), the same bolus doses may be given as in those with normal renal function but the infusion dose should be reduced to 1 microgram/kg per minute.

1. Gretler DD, et al. Pharmacokinetic and pharmacodynamic properties of eptifibatide in subjects with normal or impaired renal function. Clin Ther 2004; 26: 390-398.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. In patients with unstable angina (p.1157), eptifibatide has been used as an adjunct to both medical and interventional therapy. In the PURSUIT study,1 which compared eptifibatide with placebo in over 10 000 patients with ischaemic chest pain, the incidence of death and non-fatal myocardial infarction up to 30 days after treatment was reduced in those receiving eptifibatide; most patients also received aspirin and heparin and the number of percutaneous interventions was similar in each group.

Eptifibatide has also been of benefit as an adjunct to standard therapy in patients undergoing elective percutaneous interventions (see Reperfusion and Revascularisation Procedures, p.1181). In the IMPACT-II study² of over 4000 patients undergoing elective or emergency percutaneous coronary revascularisation, the incidence of death, myocardial infarction, and further unplanned coronary intervention was reduced in those receiving eptifibatide compared with placebo. Similar results were also obtained in a further study (ESPRIT)3 in patients who were undergoing percutaneous coronary revascularisation with stent implantation, and benefit was maintained at 6-month follow-up. Although most studies have given eptifibatide with unfractionated heparin, use with low-molecular-weight heparin also appears to be safe.5

In patients with acute myocardial infarction (p.1175), eptifibatide has been tried as an adjunct to thrombolysis or percutaneous intervention. In a study (INTRO AMI)6 comparing eptifibatide and thrombolysis with thrombolysis alone, early patency rates were improved in those receiving eptifibatide but there was no significant difference in outcomes at 30 days. In patients undergoing interventional therapy, an observational study⁷ found that eptifibatide was less effective than abciximab, but other studies^{8,9} have reported similar outcomes in patients treated with abciximab or eptifibatide. Positive results have also been seen with eptifibatide given in addition to thrombolytics before percutaneous intervention.

There have been reports of successful intracoronary use11 of eptifibatide, and also prolonged intravenous use12 in a patient unable to take oral antiplatelet drugs.

- The PURSUIT Trial Investigators. Inhibition of platelet glyco-protein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436–43.
- The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349: 1422–8.
- The ESPRIT Investigators. Novel dosing regimen of epitifibati-de in planned coronary stent implantation (ESPRIT): a ran-domised, placebo-controlled trial. *Lancet* 2000; 356: 2037–44.
- Correction. *ibid.* 2001; **357**: 1370.

 4. O'Shea JC, *et al.* Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT Tri-al: a randomized controlled trial. *JAMA* 2001; **285**: 2468–73. 5. Bhatt DL, *et al.* Safety of concomitant therapy with eptifibatide
- and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol* 2003; **41**: 20–5.
- 2003; 41: 20–5.
 6. Brener SJ, et al. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. J Am Coll Cardiol 2002; 39: 377–86.
 7. Deliargyris EN, et al. Superior in-hospital and 30-day outcomes
- with abciximab versus eptifibatide: a contemporary analysis of 495 consecutive percutaneous coronary interventions. *J Invasive Cardiol* 2004; **16**: 611–16.
- Sive Cartator 2004, 16: 011–10.
 S. Suleiman M, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, eptifibatide and abciximab: outcomes, complications and thrombocytopenia during percutaneous coronary intervention. J Invasive Cardiol 2003; 15: 319–23.

- 9. Raveendran G, et al. Eptifibatide vs abciximab as adjunctive therapy during primary percutaneous coronary intervention for acute myocardial infarction. Mayo Clin Proc 2007; 82:
- 10. ADVANCE MI Investigators. Facilitated percutaneous coro-ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. Am Heart J 2005; 150: 116–22. Correctively 150: 150: 116–22.
- beibel, 391.
 Deibele AJ, et al. Intracoronary bolus administration of eptifibatide during percutaneous coronary stenting for non ST elevation myocardial infarction and unstable angina. J Thromb Thrombolysis 2006; 22: 47–50.
 Jaffe R, et al. Prolonged intravenous eptifibatide infusion for prevention of coronary stent thrombosis. Int J Cardiol 2007; 114: 409–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part s)
Austral: Integrilin; Belg: Integrilin; Canads: Integrilin; Chile: Integrilin; C.z.: Integrilin; Denma: Integrilin; Finz: Integrilin; Finz: Integrilin; Finz: Integrilin; Genz: Integrilin; Genz: Integrilin; Genz: Integrilin; Genz: Integrilin; Hong Kong: Integrilin; Hong: Integrilin; Neth.: Integrilin; Israel: Integrilin; Nation: Integrilin; Nation: Integrilin; Nation: Integrilin; Nation: Integrilin; Port: Integrilin; Spain: Integrilin; Swed: Integrilin; Switz: Integrilin; Singlepore: Integrilin; Spain: Integrilin; Swed: Integrilin; Switz: Integrilin; Thai: Integrilin; UK: Integrilin; Syad: Integrilin; Syad: Integrilin; UK: In tegrilin; **Spain:** Integrilin; **Swed.:** lin; **UK:** Integrilin; **USA:** Integrilin

Eritrityl Tetranitrate (rINN)

Éritrityle, Tétranitrate d'; Eritrityli Tetranitras; Eritrityltetranitrat; Eritrityylitetranitraatti; Erythritol Tetranitrate; Erythrityl Tetranitrate (USAN); Erythrol Nitrate; Erythrol Tetranitrate; Nitroerythrite; Nitroerythrol; NSC-106566; Tetranitrato de eritritilo; Tetranitrol. Butane-1,2,3,4-tetrol tetranitrate.

Эритритила Тетранитрат $C_4H_6(NO_3)_4 = 302.1.$ CAS — 7297-25-8. ATC — COIDAI3. ATC Vet — QC01DA13.

Eritrityl tetranitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296). It has been used in angina pectoris

Diluted eritrityl tetranitrate is a mixture of eritrityl tetranitrate and lactose or other suitable inert excipients, the excipients being added to minimise the risk of explosion.

Handling. Undiluted eritrityl tetranitrate can be exploded by percussion or excessive heat.

Esatenolol (rINN) ⊗

(-)-Atenolol; S-Atenolol; Ésaténolol; Esatenololum. 2-{p-[(2S)-2-Hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide.

Эзатенолол

 $C_{14}H_{22}N_2O_3 = 266.3$ CAS — 93379-54-5. ATC — C07AB11. ATC Vet - QC07AB11.

Esatenolol, the S(-)-isomer of atenolol, has been used similarly to atenolol (p.1217) in the treatment of cardiovascular disorders in usual oral doses of 25 to 100 mg daily.

◊ References.

- 1. McCoy RA, et al. Pharmacodynamics of racemic and S(-)-aten-
- McGy KA, et al. Hallmacoylanines of taceine and St-Pater-olol in humans. J Clin Pharmacol 1994; 34: 816–22.
 Clementi WA, et al. Single dose pharmacokinetics of (S)-aten-olol administered orally as a single enantiomer formulation and as a racemic mixture (Tenormin). Chirality 1994; 6: 169–74.

Esmolol Hydrochloride

(BANM, USAN, rINNM) 🛇

ASL-8052; Esmolol, Chlorhydrate d'; Esmolol Hidroklorür; Esmololi Hydrochloridum; Hidrocloruro de esmolol. Methyl 3-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]propionate drochloride.

Эсмолола Гидрохлорид

 $C_{16}H_{25}NO_4$, HCI = 331.8.

CAS — 81147-92-4 (esmolol); 84057-94-3 (esmolol); 103598-03-4 (esmolol); 81161-17-3 (esmolol hydrochloride).

ATC - C07AB09

ATC Vet - QC07AB09.

Incompatibility. Licensed product information advises against admixture of esmolol hydrochloride with sodium bicarbonate because of incompatibility. There has also been a report1 of immediate haze formation after admixture of esmolol hydrochloride with warfarin sodium.

1. Bahal SM, et al. Visual compatibility of warfarin sodium injection with selected medications and solutions, Am J Health-Syst Pharm 1997; **54:** 2599–2600.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Hypotension is the most frequently reported adverse effect associated with the infusion of esmolol hydrochloride; it generally resolves within 30 minutes once the dosage is reduced or the infusion is stopped. Local irritation at the site of infusion, inflammation, induration, and thrombophlebitis have occurred and necrosis is a hazard of extravasation. These local effects have occurred with concentrations of 20 mg/mL and it is recommended that concentrations of standard formulations should not normally exceed 10 mg/mL, particularly if given peripherally, and that the infusion should not be made into a small vein.

Effects on the CNS. Generalised tonic-clonic seizures occurred in an elderly patient given esmolol hydrochloride.1

1. Das G, Ferris JC. Generalized convulsions in a patient receiving ultra short-acting beta-blocker infusion. Drug Intell Clin Pharm 1988: 22: 484-5

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

After intravenous doses esmolol is rapidly hydrolysed by esterases in the red blood cells. Steady-state blood concentrations are reached within 30 minutes with doses of 50 to 300 micrograms/kg per minute. The time to steady state may be reduced to 5 minutes by giving an appropriate loading dose. Blood concentrations decline in a biphasic manner with a distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Esmolol has low lipid solubility and is about 55% bound to plasma proteins. It is excreted in urine, primarily as the de-esterified metabolite.

Uses and Administration

Esmolol is a cardioselective short-acting beta blocker (p.1225). It is reported to be lacking in intrinsic sympathomimetic and membrane-stabilising properties.

Esmolol is used as the hydrochloride in the management of supraventricular arrhythmias (p.1160). It is also used for the control of hypertension (p.1171) and tachycardia during the perioperative period.

Esmolol hydrochloride is given intravenously at a concentration usually not exceeding 10 mg/mL.

For the rapid temporary control of ventricular rate in patients with supraventricular arrhythmias, a loading dose of 500 micrograms/kg given over 1 minute is followed by an initial maintenance infusion of 50 micrograms/kg per minute for 4 minutes. If the response is satisfactory this maintenance infusion should be continued at 50 micrograms/kg per minute. If a suitable response is not obtained within the first 5 minutes a further loading dose of 500 micrograms/kg over 1 minute may be given and the maintenance infusion may be increased to 100 micrograms/kg per minute for 4 minutes. If necessary, this procedure may be repeated once or twice more, until a satisfactory response is obtained, increasing the maintenance infusion each time by 50 micrograms/kg per minute to a maximum of 200 micrograms/kg per minute. Little additional benefit is obtained from further increases in maintenance dosage. Once a satisfactory response is obtained infusion may be continued, if necessary, for up to 48 hours. When transferring a patient to another antiarrhythmic drug, the infusion rate of esmolol hydrochloride is reduced by 50% thirty minutes after starting the alternative drug, and may be stopped one hour after the second dose of that drug.

In the control of perioperative **hypertension** and/or tachycardia, esmolol hydrochloride may be given intravenously as follows:

- · during anaesthesia, a loading dose of 80 mg over 15 to 30 seconds followed by an infusion of 150 micrograms/kg per minute, increased as necessary up to 300 micrograms/kg per minute
- on waking from anaesthesia, an infusion of 500 micrograms/kg per minute for 4 minutes, followed by an infusion of 300 micrograms/kg per minute as required
- · postoperatively, a stepped dosage schedule, as described under control of supraventricular arrhythmias above, although maintenance infusions may be increased up to 300 micrograms/kg per minute as necessary.

♦ References.

 Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharmacokinet 1995; 28: 190-202

Tetralogy of Fallot. Beta blockers have been used in the management of tetralogy of Fallot (see under Uses of Propranolol, p.1381). The *BNFC* recommends that neonates may be given esmolol hydrochloride in an initial dose of 600 micrograms/kg by intravenous injection over 1 to 2 minutes; if necessary, this may be followed by an intravenous infusion at a dose of 300 to 900 micrograms/kg per minute.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Brevibloc; Dublon; Austral.: Brevibloc; Austria: Brevibloc; Belg.: Brevibloc; Braz.: Brevibloc; Canad.: Brevibloc; Cz.: Brevibloc, Denm.: Brevibloc; Fin.: Brevibloc; Fin.: Brevibloc; Fin.: Brevibloc; Hung.: Brevibloc; India: Miniblock; Ind.: Brevibloc; Braze: Brevibloc; Hung.: Brevibloc; Malaysia: Brevibloc; Max.: Brevibloc; Neth.: Brevibloc; Neth.: Brevibloc; NZ: Brevibloc; Port.: Brevibloc; S.Afr.: Brevibloc; NZ: Brevibloc; Port.: Brevibloc; S.Afr.: Brevibloc; NZ: Brevibloc; Port.: Brevibloc; S.Afr.: Brevibloc; NZ: Br Singapore: Brevibloc†; Spain: Brevibloc; Swed.: Brevibloc; Switz.: Brevibloc; Turk.: Brevibloc; UK: Brevibloc; USA: Brevibloc.

Etacrynic Acid (BAN, rINN) ⊗

Acide étacrynique; Ácido etacrínico; Acidum etacrynicum; Etacrynsäure; Etakrino rūgštis; Etakrinsav; Etakrynsyra; Etakryynihappo; Ethacrynic Acid (USAN); Kwas etakrynowy; Kyselina etakrynová; MK-595; NSC-85791. [2,3-Dichloro-4-(2ethylacryloyl)phenoxy]acetic acid; [2,3-Dichloro-4-(2-methylene-I-oxobutyl)phenoxylacetic acid

Этакриновая Кислота $C_{13}H_{12}CI_2O_4 = 303.1.$ CAS - 58-54-8. ATC - C03CC01.ATC Vet — QC03CC01.

$$H_3C$$
 CH_2
 CI
 CI
 CI

Pharmacopoeias. In Chin., Eur. (see p.vii), Jpn, and US.

Ph. Eur. 6.2 (Etacrynic Acid). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol. It dissolves in ammonia and in dilute solutions of alkali hydroxides and carbonates.

USP 31 (Ethacrynic Acid), A white or practically white, odourless or practically odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 1.6 of alcohol, 1 in 6 of chloroform, and 1 in 3.5 of ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Sodium Etacrynate (BANM, rINNM) ⊗

Etacrinato sódico; Étacrynate de Sodium; Etacrynate Sodium; Ethacrynate Sodium (USAN); Natrii Etacrynas; Sodium Ethacrynate.

Натрий Этакринат $C_{13}H_{11}CI_{2}NaO_{4} = 325.1.$ CAS — 6500-81-8. ATC — C03CC01. ATC Vet — QC03CC01

Pharmacopoeias. In Chin.

Pol. and US include sodium etacrynate for injection.

Stability. Solutions in water of sodium etacrynate containing the equivalent of etacrynic acid 0.1% have a pH of 6.3 to 7.7. Solutions are relatively stable at about pH 7 at room temperatures for short periods and less stable at higher pH values and temperatures. They are incompatible with solutions with a pH below 5. The injection should be protected from light.

Adverse Effects

As for Furosemide, p.1292. Gastrointestinal disturbances may be more common and severe with etacrynic acid; profuse watery diarrhoea is an indication for stopping therapy. Gastrointestinal bleeding has been associated with etacrynic acid. Tinnitus and deafness, particularly after high parenteral doses, may also be more common. Other adverse effects include confusion, fatigue. nervousness, and apprehension. Haematuria has been reported

Local irritation and pain may follow intravenous injection.

Effects on carbohydrate metabolism. Although etacrynic acid is generally considered to have less pronounced effects on carbohydrate metabolism than furosemide or the thiazide diuretics, adverse effects have been reported. Reductions in glucose tolerance¹ after etacrynic acid 200 mg daily for 6 weeks were similar to those produced by hydrochlorothiazide 200 mg daily. The effect was most pronounced in diabetic patients. Hyperosmolar hyperglycaemic coma² and symptomatic hypoglycaemia with convulsions3 have been reported in patients receiving high doses of etacrynic acid.

- 1. Russell RP, et al. Metabolic and hypotensive effects of ethacrynic acid: comparative study with hydrochlorothiazide. *JAMA* 1968; **205**: 11–16.
- 2. Cowley AJ, Elkeles RS. Diabetes and therapy with potent diuretics. Lancet 1978; i: 154.
- 3. Maher JF, Schreiner GE. Studies on ethacrynic acid in patients with refractory edema, Ann Intern Med 1965; 62: 15-29

Effects on the ears. Drug-induced deafness occurred in 2 of 184 patients given etacrynic acid intravenously. 1,2 Deafness accompanied by nystagmus was reported in a patient3 after an intravenous infusion of etacrynic acid. Symptoms resolved within 1 hour. He had previously been taking furosemide and etacrynic acid orally.

- 1. Boston Collaborative Drug Surveillance Program. Drug-induced deafness: a cooperative study. JAMA 1973; 224: 515-16.
- 2. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. Lancet 1977; i: 587-8.
- Gomolin IH, Garshick E. Ethacrynic acid-induced deafness ac-companied by nystagmus. N Engl J Med 1980; 303: 702.

Precautions

Etacrynic acid's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Etacrynic acid, especially in the form of dust, is irritating to the skin, eyes, and mucous membranes.

Interactions

As for Furosemide, p.1293. The risks of gastrointestinal bleeding may be enhanced by use of etacrynic acid with other gastric irritants or with anticoagulants.

Anticoagulants. For reference to the interaction between warfarin and etacrynic acid, see p.1430.

Pharmacokinetics

Etacrynic acid is fairly rapidly absorbed from the gastrointestinal tract. The plasma half-life is 30 to 60 minutes. It is excreted both in the bile and the urine, partly unchanged and partly in the form of metabolites. It is extensively bound to plasma proteins.

Uses and Administration

Although chemically unrelated, etacrynic acid is a loop diuretic with actions and uses similar to those of furosemide (p.1294). Etacrynic acid is used in the treatment of oedema associated with heart failure (p.1165) and with renal and hepatic disorders.

Diuresis begins within about 30 minutes after an oral dose, and lasts for about 6 to 8 hours; after intravenous injection of its sodium salt, the effects are evident within a few minutes and last for about 2 hours

In the treatment of **oedema**, the usual initial oral dose is 50 mg in the morning. The dose may be increased, if necessary, by 25- to 50-mg increments daily to the minimum effective dose. Severe cases have required gradual titration of the dose up to a maximum of 400 mg daily, but the effective range is usually between 50 and 150 mg daily. Dosage of more than 50 mg daily should be given in divided doses. All doses should be taken with food. Maintenance doses may be taken daily or intermittently.

In emergencies, such as acute pulmonary oedema, or when oral therapy cannot be given, etacrynic acid may be given intravenously. It is given as its salt, sodium etacrynate, but doses are expressed in terms of the acid. 10.7 mg of sodium etacrynate is equivalent to about 10 mg of etacrynic acid. The usual dose is $50\,mg,$ or 0.5 to $1\,mg/kg,$ as a $1\,mg/mL$ solution in glucose 5%(provided the pH is above 5) or sodium chloride 0.9%, given by slow intravenous injection either directly or into the tubing of a running infusion. Should a subsequent injection be required the site should be changed to avoid thrombophlebitis. Single doses of 100 mg have been given intravenously in critical situations. It is not suitable for subcutaneous or intramuscular injection.

For children over 2 years of age an initial dose of etacrynic acid is 25 mg daily by mouth, cautiously increased as necessary by 25 mg daily.

If very high doses of etacrynic acid are used careful laboratory control is essential as described for furosemide (p.1294; highdose therapy).

Preparations

BP 2008: Sodium Etacrynate Injection; **USP 31:** Ethacrynate Sodium for Injection; Ethacrynic Acid Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Edecrin; Austria: Edecrin; Canad.: Edecrin; Cz.: Uregyt+; Ger.: Hydromedin†; Hung.: Uregyt; Ital.: Reomax; Rus.: Uregyt (Yperur); Swed.: Edecrina†; USA: Edecrin.

Etafenone Hydrochloride (HNNM)

Étafénone, Chlorhydrate d'; Etafenoni Hydrochloridum; Hidrocloruro de etafenona; LG-11457. 2'-(2-Diethylaminoethoxy)-3phenylpropiophenone hydrochloride.

Этафенона Гидрохлорид

 $C_{21}H_{27}NO_2,HCI = 361.9.$

__ 90-54-0 (etafenone); 2192-21-4 (etafenone hy-CAS -

drochloride). ATC — CO'IDX07.

ATC Vet - QC01DX07.

Profile

Etafenone hydrochloride is a vasodilator that has been used in ischaemic heart disease.

Ethacizine

Aethacizin; Etacizin; Ethacizin; Ethacyzin; EZ-55; NIK-244. Ethyl 10-[3-(diethylamino)propionyl]phenothiazine-2-carbamate.

Этацизин

 $C_{22}H_{27}N_3O_3S = 413.5.$

- 334 | 4-33-4 (ethacizine); 57530-40-2 (ethacizine hydrochloride).