membrane-stabilising activity. Nadolol is given orally in the management of hypertension (p.1171), angina pectoris (p.1157), and cardiac arrhythmias (p.1160). It is also used in the management of hyperthyroidism (p.2165) and in the prophylactic treatment of migraine (p.616).

In the treatment of **hypertension**, nadolol is usually given in an initial dose of 40 to 80 mg once daily, increased weekly according to response to 240 mg or more daily.

In **angina pectoris**, the usual initial dose is 40 mg once daily, increased weekly according to response to usual doses of up to 160 mg daily; some patients may require up to 240 mg daily. Doses of 40 to 160 mg once daily have also been given for **cardiac arrhythmias**.

Doses of 40 to 160 mg once daily are used in **migraine** prophylaxis.

As an adjunct in the treatment of **hyperthyroidism**, doses of 80 to 160 mg once daily have been given; most patients are reported to require the higher dose.

Patients with renal impairment may require a reduction in dose (see below).

Administration in renal impairment. Nadolol is excreted mainly in the urine and doses should be reduced in patients with renal impairment, usually by increasing the dosage interval. For patients with hypertension or angina pectoris, US licensed product information recommends the following dosage intervals, based on creatinine clearance (CC):

- CC between 31 and 50 mL/minute per 1.73 m^2: give every 24 to 36 hours
- CC between 10 and 30 mL/minute per 1.73 m^2: give every 24 to 48 hours
- CC less than 10 mL/minute per 1.73 m^2: give every 40 to 60 hours.

Preparations

USP 31: Nadolol and Bendroflumethiazide Tablets; Nadolol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Corgard; ***Belg.:*** Corgard; ***Braz.:*** Corgard; ***Canad.:*** Apo-Nadol; Corgard; ***Chile:*** Corgard; ***Fr.:*** Corgard; ***Ger.:*** Solgol; ***Hong Kong:*** Apo-Nadol; Corgard†; ***Ital.:*** Corgard; ***Malaysia:*** Corgard†; ***Mex.:*** Corgard; ***NZ:*** Corgard; ***Port.:*** Anabet; ***S.Afr.:*** Corgard; ***Spain:*** Corgard; Solgol; ***Switz.:*** Corgard; ***UK:*** Corgard; ***USA:*** Corgard; ***Venez.:*** Corgard.

Multi-ingredient: ***Ger.:*** Sotaziden N; ***Mex.:*** Corgaretic; ***S.Afr.:*** Corgaretic; ***UK:*** Corgaretic†; ***USA:*** Corzide.

Nadroparin Calcium *(BAN, rINN)*

CY-216; Nadropariinikalsium; Nadroparin Kalsiyum; Nadroparin vápenatá sůl; Nadroparina cálcica; Nadroparine calcique; Nadroparinkalcium; Nadroparin-kalcium; Nadroparino kalcio druska; Nadroparinum calcicum.

Надропарин Кальций

ATC — B01AB06.
ATC Vet — QB01AB06.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Nadroparin Calcium). It is prepared by nitrous acid depolymerisation of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-*O*-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain. The mass-average molecular mass ranges between 3600 and 5000, with a characteristic value of 4300. The mass percentage of chains lower than 2000 is not more than 15%. The degree of sulfation is about 2 per disaccharide unit.
The potency is not less than 95 units and not more than 130 units of anti-factor Xa activity per mg with reference to the dried substance, and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 2.5 and 4.0.

Profile

Nadroparin calcium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation. It is also used in the management of unstable angina (p.1157).

Doses are expressed in terms of anti-factor Xa activity (anti-Xa units) although different values may be encountered in the literature depending upon the reference preparation used. For *prophylaxis* of **venous thromboembolism** during surgery, patients at moderate risk of thrombosis are given 2850 units of nadroparin calcium by subcutaneous injection daily for at least 7 days or until the patient is ambulant; the first dose is given 2 to 4 hours before the procedure. For patients at high risk of thrombosis the dose is adjusted according to body-weight. Usual doses are 38 units/kg 12 hours before surgery, 12 hours postoperatively and then daily until 3 days after the procedure; the dose is then increased by 50% to 57 units/kg daily. The total duration of treatment should be at least 10 days.

For the *treatment* of thromboembolism, nadroparin calcium is given in a dose of 85 units/kg by subcutaneous injection every 12 hours for up to 10 days. Alternatively, a dose of 171 units/kg is given once daily.

For prevention of clotting in the extracorporeal circulation during **haemodialysis** sessions lasting less than 4 hours, nadroparin calcium is given into the arterial line of the circuit at the beginning of the dialysis session. The usual dose is 2850 units for patients weighing less than 50 kg, 3800 units for patients weighing 50 to 69 kg, and 5700 units for patients weighing 70 kg or more. Doses should be reduced in patients at high risk of haemorrhage.

In the management of unstable **angina**, nadroparin calcium is given subcutaneously in a dose of 86 units/kg every 12 hours, for about 6 days. An initial dose of 86 units/kg may be given intravenously. Low-dose aspirin should also be given.

Elimination of nadroparin is prolonged in renal impairment, and doses may need to be reduced in moderate or severe impairment.

◊ References.

1. Barradell LB, Buckley MM. Nadroparin calcium: a review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs* 1992; **44:** 858–88.

Preparations

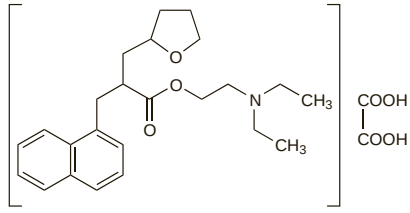
Proprietary Preparations (details are given in Part 3)
Arg.: Fraxiparine; ***Austria:*** Fraxiparin; ***Belg.:*** Fraxiparine; Fraxodi; ***Braz.:*** Fraxiparina; ***Canad.:*** Fraxiparine; ***Chile:*** Fraxiparine; ***Cz.:*** Fraxiparine; ***Fr.:*** Fraxiparine; Fraxodi; ***Ger.:*** Fraxiparin; Fraxodi; ***Gr.:*** Fraxiparine; ***Hong Kong:*** Fraxiparine; ***Hung.:*** Fraxiparine; Fraxodi; ***Indon.:*** Fraxiparine; ***Israel:*** Fraxiparine; ***Ital.:*** Fraxiparina; Fraxodi; Seledie; Seleparina; ***Malaysia:*** Fraxiparine; ***Mex.:*** Fraxiparine; Fraxodi; ***Neth.:*** Fraxiparine; Fraxodi; ***Norw.:*** Fraxiparine†; ***NZ:*** Fraxiparine†; ***Philipp.:*** Fraxiparine; ***Pol.:*** Fraxiparine; Fraxodi; ***Port.:*** Fraxiparina; Fraxodi; ***Rus.:*** Fraxiparine (Фраксипарин); ***S.Afr.:*** Fraxiparine; ***Singapore:*** Fraxiparine; ***Spain:*** Fraxiparina; ***Swed.:*** Fraxiparine†; ***Switz.:*** Fraxiforte; Fraxiparine; ***Thai.:*** Fraxiparine; ***Turk.:*** Fraxiparine; Fraxodi; ***Venez.:*** Fraxiparina.

Naftidrofuryl Oxalate *(BANM, rINNM)*

EU-1806; LS-121; Nafronyl Oxalate *(USAN)*; Naftidrofuril-hidrogén-oxalát; Naftidrofurilio-vandenilio oksalatas; Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl, hydrogénooxalate de; Naftidrofuryl, Oxalate de; Naftidrofuryli hydrogenooxalas; Naftidrofuryli Oxalas; Naftidrofuryl-oxalát; Naftidrofurylväteoxalat; Naftidrofuryylivetyoksalaatti; Oxalato de naftidrofurilo. 2-Diethylaminoethyl 3-(1-naphthyl)-2-tetrahydrofurfurylpropionate hydrogen oxalate.

Нафтидрофурила Оксалат

$C_{24}H_{33}NO_3.C_2H_2O_4$ = 473.6.
CAS — 31329-57-4 (naftidrofuryl); 3200-06-4 (naftidrofuryl oxalate).
ATC — C04AX21.
ATC Vet — QC04AX21.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Naftidrofuryl Hydrogen Oxalate; Naftidrofuryl Oxalate BP 2008). A white or almost white powder. Freely soluble in water; freely soluble or soluble in alcohol; slightly or sparingly soluble in acetone.

Adverse Effects

Naftidrofuryl oxalate given orally may cause nausea and epigastric pain. Rash has been reported occasionally. Hepatitis or hepatic failure has occurred rarely. Convulsions and depression of cardiac conduction may occur after overdosage. After intravenous use cardiac arrhythmias, hypotension, and convulsions have been reported and intravenous preparations have been withdrawn from the market (see below).

◊ In early 1995 the UK CSM published details of adverse reactions to naftidrofuryl.[1] After parenteral doses of naftidrofuryl 47 reports of 79 reactions had been received, the most serious consequences being 9 cases of cardiac arrhythmias, 3 of convulsions, and 2 of hypotension. It was also noted that 2 fatal cases of cardiac arrest had occurred in Germany after bolus intravenous doses and it was stressed that the drug must not be given as a bolus but as a slow intravenous infusion. Additionally, 16 reports, including one fatality, of hepatitis or hepatic failure associated with oral naftidrofuryl had been received although this appeared to be a rare reaction.

Later in 1995, after a review conducted in the UK and Europe, it was announced by the CSM that intravenous naftidrofuryl was to be withdrawn.[2] It was considered that the risks of cardiac and neurological toxicity outweighed the benefits of intravenous dosage in peripheral vascular disease. The oral form of naftidrofuryl would remain available.

1. Committee on Safety of Medicines/Medicines Control Agency. Adverse reactions with naftidrofuryl (Praxilene). *Current Problems* 1995; **21:** 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Withdrawal of naftidrofuryl infusion (Praxilene Forte). *Current Problems* 1995; **21:** 7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 08/05/08)

Effects on the kidneys. Calcium oxalate crystals in the renal tubules of 2 patients with acute renal failure[1] were associated with the high amounts of oxalate they had received when naftidrofuryl oxalate was given intravenously.

1. Moesch C, *et al.* Renal intratubular crystallisation of calcium oxalate and naftidrofuryl oxalate. *Lancet* 1991; **338:** 1219–20.

Uses and Administration

Naftidrofuryl oxalate is used as a vasodilator in the treatment of peripheral (p.1178) and cerebral vascular disorders (p.1165). It is also claimed to enhance cellular oxidative capacity thereby protecting cells against the results of ischaemia.

Naftidrofuryl oxalate is given orally in usual doses of 100 to 200 mg three times daily for peripheral vascular disorders and 100 mg three times daily for cerebrovascular disorders.

Naftidrofuryl oxalate has also been given parenterally. However, intravenous use has been associated with serious adverse effects (see above) and intravenous preparations have been withdrawn.

◊ References.

1. De Backer TLM, *et al.* Naftidrofuryl for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 08/05/08).

Preparations

BP 2008: Naftidrofuryl Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Iridus†; ***Austria:*** Dusodril; Naftodril; ***Belg.:*** Praxilene; ***Braz.:*** Iridux; ***Cz.:*** Enelbin; ***Fr.:*** Di-Actane; Gevatran; Naftilux; Praxilene; ***Ger.:*** Artocoron†; Azunaftil†; Dusodril; Nafti; Naftilong; ***Gr.:*** Praxilene; ***Hong Kong:*** Praxilene; ***Hung.:*** Naftilong; ***Indon.:*** Frilix; Nafoxal; Praxilene; Vascuprax; ***Irl.:*** Praxilene; ***Ital.:*** Praxilene; ***Mex.:*** Iridus; ***Philipp.:*** Praxilene; ***Port.:*** Praxilene; ***Singapore:*** Praxilene; ***Spain:*** Praxilene; ***Switz.:*** Praxilene; Sodipryl retard; ***Thai.:*** Praxilene; ***UK:*** Praxilene; ***Venez.:*** Fuxaten†; Iridus.

Nasaruplase *(rINN)*

Nasaruplasa; Nasaruplasum; Prourokinase, Glycosylated. Prourokinase (enzyme-activating) (human clone pA3/pD2/pF1 protein moiety), glycosylated.

Назаруплаза

CAS — 99821-44-0.

NOTE. The term prourokinase has been used for both nasaruplase and saruplase (p.1390).

Nasaruplase Beta *(USAN, rINN)*

Abbott-74187; ABT-187; Nasaruplasa beta; Nasaruplase Bêta; Nasaruplasum Beta. Prourokinase (enzyme-activating) human (clone pUK4/pUK18 protein moiety), glycosylated (murine cell line SP2/0).

Назаруплаза Бета

CAS — 136653-69-5.

Profile

Nasaruplase is a thrombolytic under investigation in acute ischaemic stroke.

◊ References.

1. Furlan A, *et al.* Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA* 1999; **282:** 2003–11.

Nateplase *(rINN)*

Nateplasa; Natéplase; Nateplasum. A mixture of *N*-[N^2-(*N*-glycyl-L-alanyl)-L-arginyl]plasminogen activator (human tissue-type 1-chain form, protein moiety), glycoform β (major component) and plasminogen activator (human tissue-type 1-chain form, protein moiety), glycoform β.

Натеплаза

CAS — 159445-63-3.

Profile

Nateplase is a thrombolytic related to alteplase (p.1207) that has been used in acute myocardial infarction (p.1175).

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Milyzer†.

Natriuretic Peptides ⊗

Péptidos natriuréticos.

Profile

Natriuretic peptides are endogenous substances that possess diuretic, natriuretic, and vasodilator properties. Three types are known. *Atrial natriuretic peptide* (ANP), also known as atrial natriuretic factor (ANF), atriopeptin, auriculin, or cardionatrin, is produced mainly in the cardiac atria, although another form, ularitide (urodilatin), is produced in the kidney. *Brain natriuretic peptide* (BNP, B-type natriuretic peptide) was originally isolated from brain tissue but is now known to be mainly produced by the cardiac ventricles. *C-type natriuretic peptide* (CNP) is produced by the endothelium and appears to act locally as a vasodilator but has little natriuretic effect.

Natriuretic peptides have an important physiological role in fluid and electrolyte homoeostasis and in the regulation of blood pressure, and they interact closely with other complex systems such as the renin-angiotensin-aldosterone cascade. Plasma concentrations of atrial natriuretic peptide and brain natriuretic peptide are altered in some pathological states and have been used as indicators of cardiac function. Natriuretic peptides that have been investigated for therapeutic use include anaritide, a synthetic form of atrial natriuretic peptide, and ularitide; both have been studied in acute renal failure, and ularitide has also been studied in heart failure. Recombinant forms of atrial natriuretic peptide (carperitide, p.1241) and brain natriuretic peptide (nesiritide, p.1347) are used in the management of acute heart failure.

The currently available natriuretic peptides have short half-lives and have to be given parenterally. Other approaches to manipulating their effects have been investigated, including the use of atriopeptidase inhibitors (neutral endopeptidase inhibitors; neutral metalloendopeptidase inhibitors), such as candoxatrilat and ecadotril (sinorphan) to prolong the half-life of endogenous atrial natriuretic peptide. Compounds such as omapatrilat (p.1361) that inhibit both neutral endopeptidase and angiotensin-converting enzyme are also being studied.

◊ References.

1. Tan ACITL, *et al.* Atrial natriuretic peptide: an overview of clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 1993; **24:** 28–45.
2. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart* 1996; **76** (suppl 3): 36–44.
3. Wilkins MR, *et al.* The natriuretic-peptide family. *Lancet* 1997; **349:** 1307–10.
4. Levin ER, *et al.* Natriuretic peptides. *N Engl J Med* 1998; **339:** 321–8.
5. Lewis J, *et al.* Atrial natriuretic factor in oliguric acute renal failure: Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis* 2000; **36:** 767–74.
6. Forssmann W, *et al.* The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001; **51:** 450–62.
7. de Lemos JA, *et al.* B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003; **362:** 316–22.
8. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; **92:** 843–9.
9. Mitrovic V, *et al.* Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006; **27:** 2823–32.
10. Lüss H, *et al.* Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008; **155:** 1012.e1–8.

Nebivolol *(BAN, USAN, rINN)* ⊗

Narbivolol; Nébivolol; Nebivololi; Nebivololum; R-65824. (1*RS*,1′*RS*)-1,1′-[(2*RS*,2′*SR*)-Bis(6-fluorochroman-2-yl)]-2,2′-iminodiethanol.

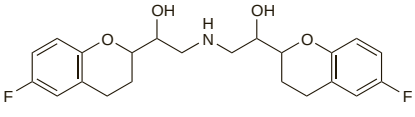
Небиволол

$C_{22}H_{25}F_2NO_4$ = 405.4.

CAS — 99200-09-6; 118457-14-0.

ATC — C07AB12.

ATC Vet — QC07AB12.



Nebivolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de nebivolol; Nébivolol, Chlorhydrate de; Nebivololi Hydrochloridum; R-67555; R-067555.

Небиволола Гидрохлорид

$C_{22}H_{25}F_2NO_4$,HCl = 441.9.

CAS — 169293-50-9; 152520-56-4.

ATC — C07AB12.

ATC Vet — QC07AB12.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

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

Pharmacokinetics

Nebivolol is rapidly absorbed after oral doses. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, *N*-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolisers the elimination half-life of nebivolol is about 10 hours and that of the hydroxy metabolites is about 24 hours. Peak plasma concentrations of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.

Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and faeces, almost entirely as metabolites. Nebivolol is distributed into breast milk in *animals*.

Uses and Administration

Nebivolol is a cardioselective beta blocker (p.1225). It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Nebivolol is used in the management of hypertension (p.1171), and as an adjunct to standard therapy in patients aged 70 years and older with stable chronic heart failure (p.1165). It is given orally as the hydrochloride although doses are expressed in terms of the base; 5.45 mg of nebivolol hydrochloride is equivalent to about 5 mg of base.

In **hypertension** the usual initial dose of nebivolol is 5 mg once daily. US licensed product information allows the dose to be increased, if necessary, at intervals of 2 weeks, to a maximum dose of 40 mg once daily. Dosage reduction may be necessary in the elderly and in patients with hepatic or renal impairment (see below).

In **heart failure** the initial dose of nebivolol is 1.25 mg once daily. If tolerated, the dose should be doubled every 1 to 2 weeks up to a maximum of 10 mg once daily.

◊ Reviews.

1. Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006; **66:** 1389–1409.
2. Veverka A, *et al.* Nebivolol: a third-generation β-adrenergic blocker. *Ann Pharmacother* 2006; **40:** 1353–60.
3. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. *Drugs* 2007; **67:** 1097–1107.
4. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory β -blocker. *J Clin Pharmacol* 2008; **48:** 225–39.

Administration in the elderly. UK licensed product information states that, for hypertension, patients over 65 years of age should be given an initial dose of 2.5 mg of nebivolol once daily, increased to 5 mg once daily if required.

Administration in hepatic impairment. UK licensed product information contra-indicates the use of nebivolol in patients with hepatic impairment. In the USA, licensed product information also contra-indicates nebivolol in severe hepatic impairment (Child-Pugh higher than class B) but patients with moderate hepatic impairment may be given nebivolol for hypertension in an initial oral dose of 2.5 mg once daily, increased with caution if required.

Administration in renal impairment. UK licensed product information states that in hypertension the initial dose of nebivolol should be reduced to 2.5 mg once daily in patients with renal impairment, increased to 5 mg once daily for maintenance if required. US licensed product information similarly recommends an initial dose of 2.5 mg once daily in patients with severe renal impairment (creatinine clearance below 30 mL/minute); the dose may be increased cautiously if required.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nebilet; ***Austria:*** Nomexor; ***Belg.:*** Nobiten; ***Chile:*** Nebilet; ***Cz.:*** Nebilet; Nebispes; ***Fr.:*** Nebilox; Temerit; ***Ger.:*** Nebilet; ***Gr.:*** Lobivon; ***Hung.:*** Nebilet; ***India:*** Nodon; ***Irl.:*** Nebilet; ***Ital.:*** Lobivon; Nebilox; ***Neth.:*** Hypoloc; Lobivon; Nebilet; Nebiloc; ***Pol.:*** Nebilet; ***Port.:*** Hypoloc; Nebilet; ***Rus.:*** Nebilet (Небилет); ***S.Afr.:*** Nebilet; ***Singapore:*** Nebilet; ***Spain:*** Lobivon; Nebilet; Nebilox; Silostar; ***Switz.:*** Nebilet; ***Thai.:*** Nebilet; ***Turk.:*** Vasoxen; ***UK:*** Nebilet; ***USA:*** Bystolic; ***Venez.:*** Nebilet.

Nesiritide Citrate *(USAN, rINNM)* ⊗

Citrato de nesiritida; Nésiritide, Citrate de; Nesiritidi Citras.

Незиритида Цитрат

$C_{143}H_{244}N_{50}O_{42}S_4$,x$C_6H_8O_7$.

CAS — 124584-08-3 (nesiritide); 189032-40-4 (nesiritide citrate).

ATC — C01DX19.

ATC Vet — QC01DX19.

Incompatibility. The manufacturer states that nesiritide injection is physically and/or chemically incompatible with heparin, insulin, sodium etacrynate, bumetanide, enalaprilat, hydralazine, furosemide, and the preservative sodium metabisulfite. Nesiritide binds to heparin and should not be given through heparin-coated central catheters.

Adverse Effects and Precautions

The most common adverse effects of nesiritide relate to vasodilatation and include hypotension, headache, and dizziness. Nausea and vomiting, abdominal pain, back pain, angina pectoris, insomnia, and anxiety, have also been reported. Cardiac arrhythmias have occurred but may be associated with the underlying condition. Adverse effects on renal function have been reported. If hypotension occurs the infusion of nesiritide should be stopped or the dose reduced and general supportive measures should be used; the hypotension may persist for several hours.

Nesiritide should not be used as primary therapy in patients with cardiogenic shock or with hypotension. It is not recommended in patients with low cardiac filling pressures or in those for whom vasodilators are inappropriate, such as those with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade.

Effects on the kidneys. Nesiritide has both haemodynamic and neurohormonal effects on the kidneys and has been reported to worsen renal function. A meta-analysis[1] found that nesiritide significantly increased the risk of worsening renal function in patients with acute heart failure, and there is some evidence[2] that this may be related to the duration of treatment. However, a randomised trial[3] in patients with acute heart failure and pre-existing renal impairment found that the effect of nesiritide on renal function was neutral.

1. Sackner-Bernstein JD, *et al.* Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; **111:** 1487–91. Correction. *ibid.*; 2274.
2. Chow SL, *et al.* Effect of nesiritide infusion duration on renal function in acutely decompensated heart failure patients. *Ann Pharmacother* 2007; **41:** 556–61.
3. Witteles RM, *et al.* Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; **50:** 1835–40.

Effects on mortality. Although nesiritide improves haemodynamics in patients with acute decompensated heart failure, its effects on mortality are controversial.[1] A retrospective study[2] comparing nesiritide with inotrope therapy or glyceryl trinitrate in patients with acute decompensated heart failure found a similar risk of in-hospital mortality with nesiritide and glyceryl trinitrate, which was significantly lower than the risk with inotrope therapy. However, a meta-analysis[3] of controlled studies comparing nesiritide with non-inotrope control therapy found that there was a trend to higher mortality at 30 days in patients given nesiritide; the results were not statistically significant, but became so after correction of the number of deaths in one of the studies.[4] A later meta-analysis[5] also found a trend towards increased mortality with nesiritide at 30 days, but the results again were not statistically significant, and there was no difference in mortality between nesiritide and control patients at 180 days.

1. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; **30:** 765–81.
2. Abraham WT, *et al.* In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46:** 57–64.
3. Sackner-Bernstein JD, *et al.* Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293:** 1900–5.
4. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006; **296:** 1465–6.
5. Arora RR, *et al.* Short and long-term mortality with nesiritide. *Am Heart J* 2006; **152:** 1084–90.

Interactions

The risk of hypotension may be increased in patients receiving nesiritide with other drugs that lower blood pressure.