Fondaparinux Sodium *(BAN, USAN, rINN)*

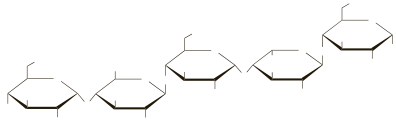
Fondaparin Sodium; Fondaparinuks Sodyum; Fondaparinuuksinatrium; Fondaparinux sódico; Fondaparinux Sodique; Fondaparinuxnatrium; Fondaparinuxum Natricum; Fondaparinuxum Natrium; Org-31540; SR-90107A.

Фондапаринукс Натрия

CAS — 114870-03-0.

ATC — B01AX05.

ATC Vet — QB01AX05.



(fondaparinux)

Adverse Effects

As for Heparin, p.1301.

Treatment of Adverse Effects

If bleeding occurs fondaparinux should be stopped and appropriate therapy given. Unlike heparin, there is no specific antidote for fondaparinux (but see below).

Overdosage. Activated eptacog alfa (recombinant factor VIIa) given 2 hours after an injection of fondaparinux was found[1] in healthy subjects to normalise coagulation times and thrombin generation for up to 6 hours, suggesting that it may be useful to treat bleeding complications, or if acute surgery is needed.

1. Bijsterveld NR, *et al.* Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; **106:** 2550–54.

Precautions

As for Heparin, p.1303.

Fondaparinux should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) in the presence of fondaparinux itself.

Fondaparinux is contra-indicated in severe renal impairment, and special care is required in patients with body-weight below 50 kg.

Interactions

As for Heparin, p.1303.

Pharmacokinetics

After subcutaneous injection fondaparinux sodium is rapidly and completely absorbed, with bioavailability of 100%. It is extensively bound in plasma, predominantly to antithrombin III. It is excreted in the urine, with 64 to 77% of a dose excreted unchanged. The elimination half-life is between 17 and 21 hours, but is prolonged in patients with renal impairment, in the elderly, and in those weighing less than 50 kg.

◊ References.

1. Donat F, *et al.* The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet* 2002; **41** (suppl 2): 1–9.
2. Paolucci F, *et al.* Fondaparinux sodium mechanism of action: identification of specific binding to purified and human plasma-derived proteins. *Clin Pharmacokinet* 2002; **41** (suppl 2): 11–18.

Pregnancy. Although an *in vitro* study[1] reported that fondaparinux does not cross the placenta, a small study[2] in pregnant women who had received fondaparinux found that anti-factor Xa activity was elevated in umbilical cord blood, suggesting that a small amount of placental transfer had taken place.

1. Lagrange F, *et al.* Fondaparinux sodium does not cross the placental barrier: study using the in-vitro human dually perfused cotyledon model. *Clin Pharmacokinet* 2002; **41** (suppl 2): 47–9.
2. Dempfle C-EH. Minor transplacental passage of fondaparinux in vivo. *N Engl J Med* 2004; **350:** 1914–15.

Uses and Administration

Fondaparinux is a synthetic pentasaccharide that acts as a selective inhibitor of activated factor X. It is used as the sodium salt as an anticoagulant in the management of venous thromboembolism (p.1189), unstable angina (p.1157), and acute myocardial infarction (p.1175). It has also been used in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Adverse Effects of Heparin, p.1302).

For *prophylaxis* of **venous thromboembolism** in abdominal and orthopaedic surgery, fondaparinux sodium is given by subcutaneous injection in a dose of 2.5 mg once daily, starting 6 to 8 hours after surgery and continued for at least 5 to 9 days, or up to 32 days in hip fracture. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6 to 14 days.

In the initial *treatment* of venous thromboembolism, fondaparinux sodium is given by subcutaneous injection once daily at a dose of 5 mg for patients weighing less than 50 kg, 7.5 mg for weight 50 to 100 kg, and 10 mg for weight over 100 kg. Treatment is usually continued for 5 to 9 days, and at least until oral anticoagulation is established.

Fondaparinux is also used in **unstable angina** and acute ST-elevation **myocardial infarction**, but is only indicated in patients for whom urgent percutaneous coronary intervention is not planned. It is given in a dose of 2.5 mg subcutaneously once daily for up to 8 days, with the first dose given intravenously in acute ST-elevation myocardial infarction. Heparin should be given at the time of the procedure if percutaneous coronary intervention is performed and fondaparinux should be restarted when clinically appropriate.

Doses of fondaparinux may need to be reduced in patients with renal impairment (see below).

◊ References.

1. Keam SJ, Goa KL. Fondaparinux sodium. *Drugs* 2002; **62:** 1673–85.
2. Tran AH, Lee G. Fondaparinux for prevention of venous thromboembolism in major orthopedic surgery. *Ann Pharmacother* 2003; **37:** 1632–43.
3. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; **349:** 1695–1702.
4. Reynolds NA, *et al.* Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. *Drugs* 2004; **64:** 1575–96.
5. Büller HR, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; **140:** 867–73.
6. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295:** 1519–30.
7. Cohen AT, *et al.* ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Abridged version: *BMJ* 2006; **332:** 325–9. Full version: http://www.bmj.com/cgi/reprint/332/7537/325 (accessed 14/05/08)
8. Yusuf S, *et al.* Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354:** 1464–76.
9. Efird LE, Kockler DR. Fondaparinux for thromboembolic treatment and prophylaxis of heparin-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 1383–7.

Administration in renal impairment. Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. US licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 30 mL/minute, and advises caution in those with CC between 30 and 50 mL/minute. UK licensed product information contra-indicates its use in patients with creatinine clearance (CC) below 20 mL/minute; for patients with CC between 20 and 50 mL/minute a subcutaneous dose of 1.5 mg once daily is recommended for prophylaxis of venous thromboembolism, but no dosage alteration is required for unstable angina or myocardial infarction.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Arixtra; ***Belg.:*** Arixtra; ***Braz.:*** Arixtra; ***Canad.:*** Arixtra; ***Cz.:*** Arixtra; ***Denm.:*** Arixtra; ***Fin.:*** Arixtra; ***Fr.:*** Arixtra; ***Ger.:*** Arixtra; ***Gr.:*** Arixtra; ***Hong Kong:*** Arixtra†; ***Indon.:*** Arixtra; ***Ital.:*** Arixtra; ***Malaysia:*** Arixtra; ***Mex.:*** Arixtra; ***Neth.:*** Arixtra; Quixidar; ***Norw.:*** Arixtra; ***NZ:*** Arixtra†; ***Pol.:*** Arixtra; ***Port.:*** Arixtra; Quixidar†; ***Rus.:*** Arixtra (Арикстра); ***Singapore:*** Arixtra; ***Spain:*** Arixtra; ***Swed.:*** Arixtra; ***Switz.:*** Arixtra; ***Thai.:*** Arixtra; ***UK:*** Arixtra; ***USA:*** Arixtra.

Fosinopril Sodium *(BANM, USAN, rINNM)*

Fosinopriilinatrium; Fosinopril sódico; Fosinopril sodique; Fosinopril Sodyum; Fosinoprilnatrium; Fosinoprilum natricum; Natrii Fosinoprilum; SQ-28555. (4*S*)-4-Cyclohexyl-1-{[(*RS*)-2-methyl-1-(propionyloxy)propoxy]-(4-phenylbutyl)phosphinylacetyl}-L-proline sodium.

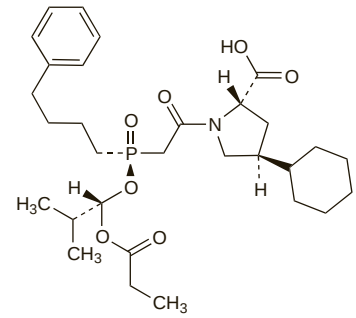
Натрий Фозиноприл

$C_{30}H_{45}NNaO_7P$ = 585.6.

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.



(fosinopril)

Pharmacopoeias. In *US*.

USP 31 (Fosinopril Sodium). Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat are achieved about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

◊ References.

1. Singhvi SM, *et al.* Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; **25:** 9–15.
2. Kostis JB, *et al.* Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; **58:** 660–5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with varying degrees of impairment,[1-5] including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al.* Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; **49:** 457–67.
2. Gehr TWB, *et al.* Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; **41:** 165–9.
3. Sica DA, *et al.* Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; **20:** 420–7.
4. Gehr TWB, *et al.* The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; **45:** 431–6.
5. Greenbaum R, *et al.* Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; **49:** 23–31.

Uses and Administration

Fosinopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Fosinopril owes its activity to fosinoprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 2 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Fosinopril is given orally as the sodium salt.

In the treatment of **hypertension**, the initial dose of fosinopril sodium is 10 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 10 to 40 mg once daily. In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Fosinopril sodium is given in an initial dose of 10 mg once daily and, if well tolerated, increased to a maximum of 40 mg once daily. An initial dose of 5 mg may be given in patients at high risk of hypotension.

◊ Reviews.

1. Murdoch D, McTavish D. Fosinopril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in essential hypertension. *Drugs* 1992; **43:** 123–40.
2. Wagstaff AJ, *et al.* Fosinopril: a reappraisal of its pharmacology and therapeutic efficacy in essential hypertension. *Drugs* 1996; **51:** 777–91.
3. Davis R, *et al.* Fosinopril: a review of its pharmacology and clinical efficacy in the management of heart failure. *Drugs* 1997; **54:** 103–16.

Preparations

USP 31: Fosinopril Sodium and Hydrochlorothiazide Tablets; Fosinopril Sodium Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Fosipril; Monace; Monopril; ***Austria:*** Fositens; ***Belg.:*** Fosinil; ***Braz.:*** Monopril; ***Canad.:*** Monopril; ***Chile:*** Monopril; ***Cz.:*** Apo-Fosinop; Fosinogen; Monopril; ***Denm.:*** Monopril; ***Fr.:*** Fozitec; ***Ger.:*** Dynacil; Fosinorm; ***Gr.:*** Monopril; Sinopril†; ***Hong Kong:*** Monopril; ***Hung.:*** Monopril; Noviform; ***India:*** Fovas; ***Indon.:*** Acenor-M; ***Israel:*** Vasopril†; ***Ital.:*** Eliten; Fosipres; Tensogard; ***Malaysia:*** Monopril†; ***Mex.:*** Monopril; ***Neth.:*** NewAce; ***Philipp.:*** BPNorm; ***Pol.:*** Monopril; ***Port.:*** Fositen; ***Rus.:*** Fosicard (Фозикард); Monopril (Моноприл); ***S.Afr.:*** Monopril; ***Singapore:*** Monopril; ***Spain:*** Fosinil†; Fositens; Hiperlex; Tenso Stop; Tensocardil; ***Swed.:*** Monopril; ***Switz.:*** Fositen; ***Thai.:*** Monopril; ***Turk.:*** Monopril; ***UAE:*** Fosipril; ***UK:*** Staril; ***USA:*** Monopril; ***Venez.:*** Monopril.

Multi-ingredient: ***Austral.:*** Monoplus; ***Austria:*** Aceplus; Fosicomb; ***Belg.:*** Foside†; ***Braz.:*** Monoplus; ***Chile:*** Monopril Plus; ***Cz.:*** Foprin Plus H; ***Fr.:*** Fozíretic; ***Ger.:*** Dynacil comp; Fosinorm comp; ***Gr.:*** Fozide; Monoplus†; ***Hung.:*** Duopril; ***Israel:*** Vasopril Plus†; ***Ital.:*** Elidiur; Fosicombi; Tensozide; ***Neth.:*** Diurace; ***Port.:*** Fositen Plus; ***Rus.:*** Fosicard H (Фозикард H); Fozide (Фозид); ***S.Afr.:*** Monozide; ***Spain:*** Fositens Plus; Hiperlex Plus; Tenso Stop Plus; ***Swed.:*** Monopril comp†; ***Switz.:*** Fosicomp; ***Thai.:*** Monoplus; ***Turk.:*** Monopril Plus; ***USA:*** Monopril-HCT; ***Venez.:*** Monopril Plus.

Furosemide *(BAN, USAN, rINN)* ⊗

Frusemide; Furosemid; Furosemida; Furosémide; Furosemidi; Furosemidum; Furoszemid; Furozemidas; LB-502. 4-Chloro-*N*-furfuryl-5-sulphamoylanthranilic acid.

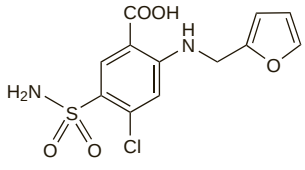
Фуросемид

$C_{12}H_{11}ClN_2O_5S$ = 330.7.

CAS — 54-31-9.

ATC — C03CA01.

ATC Vet — QC03CA01.



NOTE. Compounded preparations of furosemide may be represented by the following names:

- Co-amilofruse (*BAN*)—furosemide 8 parts and amiloride hydrochloride 1 part (w/w).

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

Ph. Eur. 6.2 (Furosemide). A white or almost white, crystalline powder. Practically insoluble in water and in dichloromethane; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Furosemide). A white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; very slightly soluble in chloroform; slightly soluble in ether; soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Solutions for injection are prepared with the aid of sodium hydroxide, giving solutions with a pH of 8.0 to 9.3.

Incompatibility. Solutions of furosemide for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

Furosemide injection has been reported[1] to be visually incompatible with injections of diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, labetalol hydrochloride, midazolam hydrochloride, milrinone lactate, nicardipine hydrochloride, and vecuronium bromide. Incompatibility has also been noted with parenteral nutrient solutions,[2] with cisatracurium besilate,[3] with levofloxacin,[4] with phenylephrine,[5] and with vasopressin.[5]

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1295–1300.
3. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
4. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.
5. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; **63:** 906–8.

Stability. A study[1] showed that furosemide injection (10 mg/mL) in 25% human albumin solution was stable for 48 hours at room temperature when protected from light, and for 14 days under refrigeration. No bacterial or fungal growth was found.

1. Elwell RJ, *et al.* Stability of furosemide in human albumin solution. *Ann Pharmacother* 2002; **36:** 423–6.

Adverse Effects

Most adverse effects of furosemide occur with high doses, and serious effects are uncommon. The most common adverse effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, and hypochloraemic alkalosis, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, oliguria, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolaemia and dehydration may occur, especially in the elderly. Because of their shorter duration of action, the risk of hypokalaemia may be less with loop diuretics such as furosemide than with thiazide diuretics. Unlike the thiazides, furosemide increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants.

Furosemide may cause hyperuricaemia and precipitate gout in some patients. It may provoke hyperglycaemia and glycosuria, but probably to a lesser extent than the thiazide diuretics.

Pancreatitis and cholestatic jaundice seem to occur more often than with the thiazides. Other adverse effects include blurred vision, yellow vision, dizziness, headache, and orthostatic hypotension. Other adverse effects occur rarely. Skin rashes and photosensitivity reactions may be severe; hypersensitivity reactions include interstitial nephritis and vasculitis; fever has also been reported. Bone marrow depression may occur: there have been reports of agranulocytosis, thrombocytopenia, and leucopenia. Tinnitus and deafness may occur, in particular during rapid high-dose parenteral furosemide. Deafness may be permanent, especially in patients taking other ototoxic drugs.

Incidence of adverse effects. In a survey of 553 hospital inpatients[1] receiving furosemide 220 patients (40%) had 480 adverse reactions. Electrolyte disturbances occurred in 130 (23.5%) patients and extracellular volume depletion in 50 (9%). Adverse reactions were more common in those with liver disease, and hepatic coma occurred in 20 patients with hepatic cirrhosis. A similar survey in 585 hospital inpatients[2] revealed 177 adverse effects in 123 (21%). These included volume depletion in 85 patients (14.5%), hypokalaemia in 21 (3.6%), and hyponatraemia in 6 (1%). Hypokalaemia was considered to be life-threatening in 2 patients. Hyperuricaemia occurred in 54 patients (9.2%), of whom 40 also had volume depletion, and clinical gout developed in 2.

1. Naranjo CA, *et al.* Frusemide-induced adverse reactions during hospitalization. *Am J Hosp Pharm* 1978; **35:** 794–8.
2. Lowe J, *et al.* Adverse reactions to frusemide in hospital inpatients. *BMJ* 1979; **2:** 360–2.

Carcinogenicity. See under Hydrochlorothiazide, p.1308.

Effects on the ears. Ototoxicity and deafness during furosemide therapy is most frequently associated with elevated blood concentrations resulting from rapid intravenous infusion[1] or delayed excretion in patients with renal impairment.[2] Of 29 cases of furosemide-induced deafness reported to the FDA[3] in the USA, most patients had renal disease or had received the drug intravenously. Eight patients had also received another ototoxic drug. However, deafness occurred in 11 patients after oral use, and in 4 of these hearing loss occurred in the absence of renal disease or other ototoxic drugs. Hearing loss was generally transient, lasting from one-half to 24 hours, but permanent hearing loss occurred in 3 patients, one of whom had taken furosemide orally. Deafness was not always associated with high doses; six patients had received a total of 200 mg or less of furosemide.

See also Precautions, below.

1. Heidland A, Wigand ME. Einfluss hoher Furosemiddosen auf die Gehörfunktion bei Urämie. *Klin Wochenschr* 1970; **48:** 1052–6.
2. Schwartz GH, *et al.* Ototoxicity induced by furosemide. *N Engl J Med* 1970; **282:** 1413–14.
3. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med* 1979; **91:** 744–5.

Effects on electrolyte balance. ***CALCIUM.*** Furosemide increases renal calcium excretion. There is a danger of hypocalcaemic tetany during furosemide use in hypoparathyroid patients[1] and it has also been reported[2] in a patient with latent hypoparathyroidism following thyroidectomy.

The decrease in serum-calcium concentrations could also induce hyperparathyroidism. In a study involving 36 patients with heart failure, furosemide was associated with elevations in both parathyroid hormone and alkaline phosphatase concentrations, possibly indicating accelerated bone remodelling such as that found in primary hyperparathyroidism.[3]

For reports of hypercalciuria, rickets, renal calculi, and hyperparathyroidism in neonates given furosemide, see Effects in Infants and Neonates, below.

1. Gabow PA, *et al.* Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. *Ann Intern Med* 1977; **86:** 579–81.
2. Bashey A, MacNee W. Tetany induced by frusemide in latent hypoparathyroidism. *BMJ* 1987; **295:** 960–1.
3. Elmgreen J, *et al.* Elevated serum parathyroid hormone concentration during treatment with high ceiling diuretics. *Eur J Clin Pharmacol* 1980; **18:** 363–4.

MAGNESIUM, POTASSIUM, AND SODIUM. For discussions of the effects of diuretics on these electrolytes see under the Adverse Effects of Hydrochlorothiazide, p.1308.

Effects in infants and neonates. Furosemide is commonly used in the treatment of cardiac and pulmonary disorders in premature infants and neonates. This age group appears to be particularly susceptible to adverse effects arising from the increase in urinary calcium excretion which occurs during long-term use. Increases in parathyroid hormone concentration[1,2] and evidence of bone resorption[1,3] support the suggestion that the increased calcium loss causes secondary hyperparathyroidism. There have been reports of decreased mineral content of bone,[1,3] rickets,[4] fractures,[3] and renal calcification.[1,5-7] An observation[5] that renal calcification could be reversed by the addition of a thiazide diuretic was supported by other workers.[6] There is evidence[8] that furosemide-related renal calcifications in very low birth-weight infants might be associated with long-term renal impairment. Renal calcification has also been reported after furosemide use in older infants.[9]

It has been suggested[10] that a sodium deficit in infants given furosemide for heart failure may contribute to a failure to thrive.

Concern has been expressed over the finding[11] that furosemide use in premature infants with respiratory distress syndrome increases the incidence of patent ductus arteriosus. The mechanism is thought to be connected with stimulation of renal prostaglandin E_2. However, the increased incidence of patent ductus arteriosus did not adversely affect the mortality in infants given furosemide, and a subsequent study[12] failed to find any increase in the incidence of patent ductus arteriosus in infants treated with furosemide compared with a control group. Paradoxically, furosemide has been used in the management of delayed closure of ductus (see Patent Ductus Arteriosus under Uses and Administration, below). There is a possibility that furosemide may not be