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 In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.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.

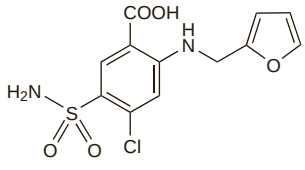
Фуросемид

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

effective in infants given indometacin[13] but it can prevent the decline in urine output which occurs during indometacin use.[14,15]

1. Venkataraman PS, *et al.* Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child* 1983; **187:** 1157–61.
2. Vileisis RA. Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease. *Pediatrics* 1990; **85:** 316–22.
3. Morgan MEI, Evans SE. Osteopenia in very low birthweight infants. *Lancet* 1986; **ii:** 1399–1400.
4. Chudley AE, *et al.* Nutritional rickets in 2 very low birthweight infants with chronic lung disease. *Arch Dis Child* 1980; **55:** 687–90.
5. Hufnagle KG, *et al.* Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982; **70:** 360–3.
6. Noe HN, *et al.* Urolithiasis in pre-term neonates associated with furosemide therapy. *J Urol (Baltimore)* 1984; **132:** 93–4.
7. Pearse DM, *et al.* Sonographic diagnosis of furosemide-induced nephrocalcinosis in newborn infants. *J Ultrasound Med* 1984; **3:** 553–6.
8. Downing GJ, *et al.* Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years. *J Pediatr* 1992; **120:** 599–604.
9. Alon US, *et al.* Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. *J Pediatr* 1994; **125:** 149–51.
10. Salmon AP, *et al.* Sodium balance in infants with severe congestive heart failure. *Lancet* 1989; **ii:** 875.
11. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
12. Yeh TF, *et al.* Early furosemide therapy in premature infants (≤ 2000 gm) with respiratory distress syndrome: a randomized controlled trial. *J Pediatr* 1984; **105:** 603–9.
13. Friedman Z, *et al.* Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low-birth-weight infants. *J Pediatr* 1978; **93:** 512–15.
14. Yeh TF, *et al.* Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. *J Pediatr* 1982; **101:** 433–7.
15. Nahata MC, *et al.* Furosemide can prevent decline in urine output in infants receiving indomethacin for patent ductus closure: a multidose study. *Infusion* 1988; **12:** 11–12 and 15.

Effects on lipid metabolism. Most studies into the effects of diuretics on blood-lipid concentrations have used thiazides (see Hydrochlorothiazide, p.1308). The few studies into the effects of furosemide suggest that, like thiazides, it may adversely influence blood-lipid concentrations during short-term use.[1]

1. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins I: diuretics. *Drugs* 1986; **32:** 260–78.

Precautions

Precautions and contra-indications for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309). Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. Furosemide should not be given in pre-comatose states associated with hepatic cirrhosis. It should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

To reduce the risk of ototoxicity, licensed product information recommends that furosemide should not be injected intravenously at a rate exceeding 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Furosemide should be used with caution during pregnancy and breast feeding since it crosses the placenta and also appears in breast milk. Furosemide may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

Hepatic impairment. In patients with chronic heart failure and moderate liver congestion, high-dose furosemide therapy could produce increases in liver enzymes suggestive of hepatitis.[1] Special care should be taken with the dosage and mode of administration of furosemide in such patients to avoid severe ischaemic liver damage caused by a drop in systemic blood pressure.

As with the thiazides, furosemide should be avoided in patients with severe hepatic impairment.

1. Lang I, *et al.* Furosemide and increases in liver enzymes. *Ann Intern Med* 1988; **109:** 845.

Hypersensitivity. Furosemide is a sulfur-containing diuretic and hypersensitivity reactions may occur, although they are rare; cross-reactivity with other sulfur-containing drugs is also possible. However, 2 patients who had in the distant past shown serious adverse reactions to sulfur-containing diuretics were successfully treated[1] with furosemide using a rechallenge protocol. They were given an initial dose of 50 micrograms which was increased gradually each day to 20 mg by day 10, and were discharged from hospital on a maintenance dose of 40 mg twice daily. Another patient[2] with a history of sulfonamide-induced pancreatitis developed pancreatitis with furosemide, which recurred with bumetanide and torasemide and on rechallenge with furosemide. She underwent a rapid desensitisation regimen and was subsequently successfully stabilised on oral furosemide.

1. Earl G, *et al.* Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; **138:** 358–9.
2. Juang P, *et al.* Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. *Ann Pharmacother* 2006; **40:** 128–34.

Hypoparathyroidism. For comments on the possibility of hypocalcaemic tetany in hypoparathyroid patients taking furosemide, see Effects on Electrolyte Balance, above.

Infants and neonates. Caution must be exercised in using furosemide in infants, particularly for long periods. The immaturity of the renal system can result in unexpectedly high blood concentrations and extended half-lives. Fluid and electrolyte balances should therefore be monitored carefully. Neonates appear to be particularly susceptible to increases in urinary calcium concentrations after long-term use. There have also been reports[1] of an increased incidence of patent ductus arteriosus in infants given furosemide, although this did not adversely affect mortality.

Secondly, several studies[2-4] have shown furosemide to be a potent displacer of bilirubin from albumin binding sites and it should be used with caution in jaundiced infants. On a molar basis chlorothiazide, furosemide, and etacrynic acid were at least as potent as sulfafurazole in displacing bilirubin from albumin.[3] Doses of furosemide 1 mg/kg probably do not produce a significant increase in free bilirubin in most jaundiced infants,[3,4] although doses greater than 1.5 mg/kg or repeated dosing could potentially do so.[4] Chlorothiazide 15 to 20 mg/kg would not be an appropriate alternative to furosemide[3] since it could produce higher plasma bilirubin concentrations in jaundiced infants.

In addition, there is some evidence from an *in vitro* study[5] that bilirubin may displace furosemide from binding sites to a greater extent in neonates than in adults. The clearance of furosemide is much slower in neonates than in adults, with an eightfold prolongation in plasma half-life, and this should be taken into account during repeat dosing.[4]

1. Green TP, *et al.* Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983; **308:** 743–8.
2. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1977; **90:** 642–6.
3. Wennberg RP, *et al.* Displacement of bilirubin from human albumin by three diuretics. *J Pediatr* 1977; **90:** 647–50.
4. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.
5. Viani A, Pacifici GM. Bilirubin displaces furosemide from serum protein: the effect is greater in newborn infants than adult subjects. *Dev Pharmacol Ther* 1990; **14:** 90–5.

Porphyria. Furosemide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The interactions of furosemide that are due to its effects on fluid and electrolyte balance are similar to those of hydrochlorothiazide (see p.1309).

Furosemide may enhance the nephrotoxicity of cephalosporin antibacterials such as cefalotin and can enhance the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs.

Aliskiren. Licensed product information for aliskiren states that it may significantly decrease furosemide concentrations.

Antiepileptics. The diuretic effect of furosemide has been shown to be substantially reduced by mixed antiepileptic therapy that included *phenytoin*.[1,2] The mean diuretic effect of furosemide 20 mg or 40 mg by mouth in patients on such therapy was 68% and 51% that of healthy controls respectively.[1]

For the effect of furosemide on *phenobarbital*, see p.493.

Symptomatic hyponatraemia has been associated with the use of furosemide or hydrochlorothiazide with *carbamazepine*.[3]

1. Ahmad S. Renal insensitivity to frusemide caused by chronic anticonvulsant therapy. *BMJ* 1974; **3:** 657–9.
2. Fine A, *et al.* Malabsorption of frusemide caused by phenytoin. *BMJ* 1977; **2:** 1061–2.
3. Yassa R, *et al.* Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; **48:** 281–3.

Diuretics. Severe electrolyte disturbances may occur in patients given *metolazone* with furosemide.

Hypnotics. A syndrome of flushing, tachycardia, elevated blood pressure, and severe diaphoresis was reported after intravenous dosage of furosemide in 6 patients who had taken *cloral hydrate* orally during the preceding 24 hours.[1] The reaction recurred in 1 patient on a subsequent occasion when given both drugs but not when furosemide was used without cloral hydrate. A subsequent retrospective study[2] among 43 patients who had received both cloral hydrate and furosemide showed that 1 patient had suffered a similar reaction; of 2 further patients who had possibly been affected, 1 had subsequently taken both drugs without adverse effects. A similar interaction has been reported in an 8-year-old child.[3]

1. Malach M, Berman N. Furosemide and chloral hydrate: adverse drug interaction. *JAMA* 1975; **232:** 638–9.
2. Pevonka MP, *et al.* Interaction of chloral hydrate and furosemide: a controlled retrospective study. *Drug Intell Clin Pharm* 1977; **11:** 332–5.
3. Dean RP, *et al.* Interaction of chloral hydrate and intravenous furosemide in a child. *Clin Pharm* 1991; **10:** 385–7.

Lithium. For reports of a possible increase in plasma-lithium concentrations in patients receiving loop diuretics, see p.405.

NSAIDs. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics.[1] Use of NSAIDs with diuretics may increase the risk of nephrotoxicity, although it has also been suggested that furosemide may protect against the renal effects of *indometacin* in infants (see Effects in Infants and Neonates, above).

1. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; **30:** 32–41.

Probenecid. Probenecid has been shown[1-4] to reduce the renal clearance of furosemide, and to reduce the diuretic effect.[2,3]

1. Honari J, *et al.* Effects of probenecid on furosemide kinetics and natriuresis in man. *Clin Pharmacol Ther* 1977; **22:** 395–401.
2. Odlind B, Beermann B. Renal tubular secretion and effects of furosemide. *Clin Pharmacol Ther* 1980; **27:** 784–90.
3. Smith DE, *et al.* Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* 1980; **69:** 571–5.
4. Vree TB, *et al.* Probenecid inhibits the renal clearance of frusemide and its acyl glucuronide. *Br J Clin Pharmacol* 1995; **39:** 692–5.

Tobacco. The effects of tobacco smoking on the pharmacokinetics of furosemide have been reviewed.[1,2] Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide. However, this effect is attenuated in habitual smokers.

1. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; **17:** 90–108.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9:** 125–35.

Xanthines. For the effect of furosemide on *theophylline*, see p.1144.

Pharmacokinetics

Furosemide is fairly rapidly absorbed from the gastrointestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to 99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk. The clearance of furosemide is not increased by haemodialysis.

◊ The pharmacokinetics of furosemide have been extensively reviewed.[1-6] The development of an analytical method using HPLC with fluorescence has produced greater sensitivity and more consistent results. Absorption after oral use is erratic and is subject to large inter- and intra-individual variation. It is influenced by the dosage form, underlying disease processes, and by the presence of food. Furosemide absorption in patients with heart failure has been reported to be even more erratic than in healthy subjects. The bioavailability of furosemide from oral dosage forms is also highly variable with reported values ranging from 20 to 100%. It is influenced by factors affecting absorption but the poor solubility of furosemide does not appear to have a major influence on bioavailability and *in vitro* dissolution data may not reflect *in vivo* bioavailability. Bioavailability tends to be decreased by about 10% in patients with renal disease, and slightly increased in liver disease. Values are erratic in patients with heart disease.

Furosemide is highly bound to plasma proteins, almost exclusively to albumin. The proportion of free (unbound) furosemide is higher in patients with heart disease, renal impairment, and cirrhosis of the liver. Patients with liver disease also have an increased apparent volume of distribution which is proportionally greater than the observed decrease in protein binding. Patients with nephrotic syndrome have significant proteinuria and secondary hypoalbuminaemia. This results in reduced protein binding in the blood, particularly at higher blood concentrations, and binding to proteins present in the urine, which may account for the resistance to furosemide therapy reported in these patients.

A glucuronide metabolite of furosemide is produced in varying amounts. The site of metabolism is unknown at present. There is debate over another potential metabolite, 4-chloro-5-sulfamoyl anthranilic acid (CSA). It has been argued[3] that it is an artefact produced during the extraction procedures although there is some evidence to refute this.[4]

A half-life for furosemide in healthy subjects has generally been reported in the range of 30 to 120 minutes. In patients with end-stage renal disease the average half-life is 9.7 hours. The half-life

may be slightly longer in patients with hepatic dysfunction and a range of 50 to 327 minutes has been reported in patients with heart failure. In severe multi-organ failure the half-life may range from 20 to 24 hours.

Furosemide clearance is influenced by age, underlying disease state, and drug interactions. Clearance reduces with increasing age, probably due to declining renal function. Renal impairment in renal or cardiac disease reduces renal clearance, although this may be compensated for by increases in non-renal clearance. Hepatic impairment has little impact on clearance. Renal and non-renal clearance may be reduced by probenecid and indometacin.

The effectiveness of furosemide as a diuretic depends upon it reaching its site of action, the renal tubules, unchanged. About one-half to two-thirds of an intravenous dose or one-quarter to one-third of an oral dose are excreted unchanged, the difference being largely due to the poor bioavailability from the oral route. The effect of furosemide is more closely related to its urinary excretion than to the plasma concentration. Urinary excretion may be reduced in renal impairment due to reduced renal blood flow and reduced tubular secretion.

1. Cutler RE, Blair AD. Clinical pharmacokinetics of frusemide. *Clin Pharmacokinet* 1979; **4:** 279–96.
2. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979; **7:** 1–27.
3. Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; **17:** 1–46.
4. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
5. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part II). *Clin Pharmacokinet* 1990; **18:** 460–71.
6. Vrhovac B, *et al.* Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet* 1995; **28:** 405–18.

Infants and neonates. The half-life of furosemide in term and preterm neonates is markedly prolonged compared with that in adults.[1,2] Half-lives of 4.5 to 46 hours have been reported and it has been suggested that the prolongation may be greater in preterm than in term neonates. This effect is due primarily to immature renal function and if repeated doses are necessary over a short period accumulation may occur.[1]

1. Besunder JB, *et al.* Principles of drug biodisposition in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988; **14:** 261–86.
2. Aranda JV, *et al.* Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; **93:** 507–11.

Uses and Administration

Furosemide is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure (below), including pulmonary oedema, and with renal and hepatic disorders (but see Precautions, above) and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension (p.1171), either alone or with other antihypertensives.

Furosemide inhibits the reabsorption of electrolytes primarily in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. See Action, below, for further reference to its mechanism of action.

Administration and dosage. Furosemide's effects are evident within 30 minutes to 1 hour after an oral dose, peak at 1 to 2 hours, and last for about 4 to 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours. It is given orally, usually in the morning. Alternatively it may be given intramuscularly or intravenously as the sodium salt; doses are expressed in terms of furosemide base. 10.7 mg of furosemide sodium is equivalent to about 10 mg of furosemide base. Licensed product information recommends that whether by direct intravenous injection or by infusion the rate of intravenous dosage should not exceed 4 mg/minute although the *BNF* advises that a single dose of up to 80 mg may be given more rapidly.

Unlike the thiazide diuretics where, owing to their flat dose-response curve, very little is gained by increasing the dose, furosemide has a steep dose-response curve, which gives it a wide therapeutic range.

In the treatment of **oedema**, the usual initial oral dose is 40 mg once daily, adjusted as necessary according to response. Mild cases may respond to 20 mg daily or 40 mg on alternate days. Some patients may need doses of 80 mg or more daily given as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. In an emergency or when oral therapy cannot be given, 20 to 50 mg of furosemide may be given by slow intravenous injection; intramuscular injection may be given in exceptional cases but is not suitable for acute conditions. If necessary further doses may be given, increasing by 20-mg increments and not given more often than every 2 hours. If doses above 50 mg are required they should be given by slow intravenous infusion. For pulmonary oedema, if an initial slow intravenous injection of 40 mg does not produce a satisfactory response within one hour, a further 80 mg may be given slowly intravenously.

For children, the usual oral dose is 1 to 3 mg/kg daily up to a maximum of 40 mg daily; doses by injection are 0.5 to 1.5 mg/kg daily up to a maximum of 20 mg daily.

In the treatment of **hypertension**, furosemide is given in oral doses of 40 to 80 mg daily, either alone, or with other antihypertensives.

High-dose therapy. In the management of **oliguria** in acute or chronic renal failure where the glomerular filtration rate is less than 20 mL/minute but greater than 5 mL/minute, furosemide 250 mg diluted to 250 mL in a suitable diluent is infused over one hour. If urine output is insufficient within the next hour, this dose may be followed by 500 mg added to an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, and infused over about 2 hours. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion then a third dose of 1 g may be infused over about 4 hours. The rate of infusion should never exceed 4 mg/minute. In oliguric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant rate infusion pump with a micrometer screw-gauge adjustment; the rate should still never exceed 4 mg/minute. Patients who do not respond to a dose of 1 g probably require dialysis. If the response to either dosage method is satisfactory, the effective dose (of up to 1 g) may then be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, oral treatment may be maintained; 500 mg should be given orally for each 250 mg required by injection.

When used in chronic renal impairment, an initial oral dose of 250 mg may be given, increased, if necessary in steps of 250 mg every 4 to 6 hours to a maximum of 1.5 g in 24 hours; in exceptional cases up to 2 g in 24 hours may be given. Dosage adjustments should subsequently be made according to the patient's response.

During treatment with these high-dose forms of furosemide therapy, careful laboratory control is essential. Fluid balance and electrolytes should be carefully controlled and, in particular, in patients with shock, measures should be taken to correct the blood pressure and circulating blood volume, before commencing this type of treatment. High-dose furosemide therapy is contra-indicated in renal failure caused by nephrotoxic or hepatotoxic drugs, and in renal failure associated with hepatic coma.

Action. The mechanism of action of furosemide is not fully understood.[1] It appears to act primarily by inhibiting active reabsorption of chloride ions in the ascending limb of the loop of Henle. Urinary excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is increased; the chloride excretion exceeds that of sodium and there is an enhanced exchange of sodium for potassium leading to greater excretion of potassium. The resulting low osmolality of the medulla inhibits the reabsorption of water by the kidney. There is a possibility that furosemide may also act at a more proximal site.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance.

Furosemide has been shown to increase plasma-renin activity, plasma-noradrenaline concentrations, and plasma-arginine-vasopressin concentrations. Alterations in the renin-angiotensin-aldosterone system may play a part in the development of acute tolerance. Furosemide increases renal-prostaglandin concentrations but it is not known whether this is due to increased synthesis or inhibition of degradation or both. Prostaglandins appear to mediate the diuretic/natriuretic action. The primary effects appear to be alterations in renal haemodynamics with subsequent increases in electrolyte and fluid excretion.

The diuretic response to furosemide is related to the concentration in the urine, not to that in the plasma. Furosemide is delivered to the renal tubules by a non-specific organic acid pump in the proximal tubules.[1]

In some cases sodium intake may be sufficient to overcome the diuretic effect, and limiting sodium intake could restore responsiveness.[2]

1. Ponto LLB, Schaenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; **18:** 381–408.
2. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. *Drugs* 1985; **30:** 427–43.

Administration. Continuous intravenous infusion of loop diuretics may be more effective than intermittent intravenous bolus injection and may provide a more consistent urine flow with fewer alterations in urine balance.[1,2] Bumetanide was more effective by continuous infusion than as bolus doses in 8 patients with severe chronic renal impairment.[3] In 20 patients with chronic heart failure requiring high-dose furosemide therapy, furosemide given by continuous infusion was more effective than the same dose by bolus injection.[4] The lower plasma concentrations associated with continuous infusion may also reduce the risk of toxicity.

1. Yelton SL, *et al.* The role of continuous infusion loop diuretics. *Ann Pharmacother* 1995; **29:** 1010–14.
2. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; **40:** 1797–1803.
3. Rudy DW, *et al.* Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; **115:** 360–6.
4. Dormans TPJ, *et al.* Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; **28:** 376–82.

Ascites. Dietary sodium restriction and diuretics are mainstays of the management of cirrhotic ascites (p.1159). Spironolactone is usually the diuretic of first choice, but furosemide may be added to therapy as necessary.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids (see p.1500). Additional supportive therapy may include the use of diuretics such as furosemide.

Alternate-day therapy with oral furosemide 4 mg/kg has produced modest benefits in pulmonary status in the absence of a diuretic effect, and few adverse effects.[1] Improved pulmonary function has occurred in infants given furosemide 1 mg/kg parenterally after packed red blood cell transfusions, given to improve oxygen-carrying capacity.[2] The successful use of nebulised furosemide in a dose of 1 mg/kg has been reported;[3,4] again pulmonary status was improved without production of diuresis or renal side-effects. However, a single inhaled dose of 1 mg/kg failed to improve pulmonary mechanics in another study involving older infants with more severe disease.[5] Systematic reviews of the use of intravenous or oral,[6] or nebulised[7] diuretics in preterm infants with chronic lung disease concluded that, although there were improvements in pulmonary function, there was insufficient evidence to recommend routine use.

1. Rush MG, *et al.* Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 112–18.
2. Stefano JL, Bhutani VK. Role of furosemide therapy after booster-packed erythrocyte transfusions in infants with bronchopulmonary dysplasia. *J Pediatr* 1990; **117:** 965–8.
3. Rastogi A, *et al.* Nebulized furosemide in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; **125:** 976–9.
4. Prabhu VG, *et al.* Pulmonary function changes after nebulised and intravenous frusemide in ventilated premature infants. *Arch Dis Child* 1997; **77:** F32–F35.
5. Kugelman A, *et al.* Pulmonary effect of inhaled furosemide in ventilated infants with severe bronchopulmonary dysplasia. *Pediatrics* 1997; **99:** 71–5.
6. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 24/06/05).
7. Brion LP, *et al.* Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/05/08).

Haemolytic-uraemic syndrome. Renal failure is a possible consequence of the haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p.1076). Correction of any hypovolaemic state with adequate fluids and of oliguria by inducing diuresis with furosemide may be used to prevent this.

Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.[1] In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urate clearance.

1. Rousseau E, *et al.* Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; **34:** 22–5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p.1165) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions[1] or high doses (up to 8 g daily) of furosemide given by intravenous infusion[2,3] or orally.[3] A patient who was successfully maintained on intravenous furosemide at home has been described.[4] Combination of furosemide with thiazide diuretics[5] or metolazone[6,7] has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.[8] Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine[9] or captopril.[10] The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.[11] In elderly patients not responding adequately to low-dose furosemide together with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported[12] to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study[13] in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported[14] to augment the effect of furosemide.

1. Lawson DH, *et al.* Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; **2:** 476.
2. O'Rourke MF, *et al.* High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; **144:** 2429.
3. Gerlag PGG, van Meijel JJM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; **148:** 286–91.
4. Hattersley AT, *et al.* Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; **i:** 446.
5. Channer KS, *et al.* Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; **335:** 922–3.
6. Aravot DJ, *et al.* Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727.
7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727–8.
8. Oster JR, *et al.* Combined therapy with thiazide-type and loop diuretic agents for resistant-sodium retention. *Ann Intern Med* 1983; **99:** 405–6.
9. Nomura A, *et al.* Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; **30:** 177–82.
10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100:** 777–82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; **100:** 902–4.
12. Waterer G, Donaldson M. High-dose frusemide for cardiac failure. *Lancet* 1995; **346:** 254.
13. Cotter G, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62:** 187–93.
14. Paterna S, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2:** 305–13.

Hypercalcaemia. Hypercalcaemia (p.1668) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This primarily involves rehydration, but loop diuretics such as furosemide have been used after rehydration, to promote urinary calcium excretion. Doses used have ranged from 20 to 240 mg of furosemide daily, given intravenously.

Obstructive airways disease. In patients with *asthma*, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise[1] and external stimuli,[2,3] although it did not improve bronchial hyperresponsiveness in a 4-week study[4] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[5] A number of mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.[6] The potential for clinical applications remains unclear[6] and furosemide is not a part of the accepted schedules for the treatment of asthma (p.1108).

A small study[7] in patients with *chronic obstructive pulmonary disease* found that inhalation of furosemide relieved bronchoconstriction and dyspnoea induced by exercise.

Inhaled furosemide has also been used to relieve *dyspnoea in patients with terminal cancer*.[8]

1. Munyard P, *et al.* Inhaled frusemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; **50:** 677–9.
2. Bianco S, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; **321:** 1069–73.
3. Seidenberg J, *et al.* Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; **67:** 214–17.
4. Yates DH, *et al.* Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; **152:** 2173–5.
5. González-Sánchez R, *et al.* Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; **23:** 181–4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; **3:** 30–41.
7. Ong K-C, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169:** 1028–33.
8. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indometacin is generally given to promote closure of the ductus (see p.68).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome — see Effects in Infants and Neonates under Adverse Effects, above). A systematic review[1] of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised intracranial pressure (p.1181) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p.1866), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Preparations

BP 2008: Co-amilofruse Tablets; Furosemide Injection; Furosemide Tablets; ***USP 31:*** Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Eliur†; Errolon; Fabofurox; Frecuental†; Furagrand; Furital; Furix; Fursemida; Furtenk; Kolkin; Lasix; Nuriban; Retep; Viafurox†; ***Austral.:*** Frusehexal; Frusid; Lasix; Uremide; Urex; ***Austria:*** Fural; Furohexal; Furon; Furostad; Lasix; ***Belg.:*** Docfurose; Furotop; Lasix; ***Braz.:*** Diuremida; Diuret†; Diurit†; Diurix; Fluxil; Furesin; Furosan; Furosecord†; Furosem; Furosen†; Furosetron; Furosix; Furozix; Fursemida; Lasix; Neosemid; Normotensor†; Rovelan; Urasix; ***Canad.:*** Lasix; Novo-Semide; ***Chile:*** Asax; Lasix†; ***Cz.:*** Dryptal†; Furanthril†; Furon; Furorese; Lasix†; ***Denm.:*** Diural; Furese; Furix; Lasix; ***Fin.:*** Furesis; Furomin; Lasix; Vesix; ***Fr.:*** Lasilix; ***Ger.:*** Diurapid; durafurid†; Furanthril; Furo; Furo-Puren; Furobeta; Furogamma; Furomed; Furorese; Furosal; Fusid; Jufurix; Lasix; Odemase†; ***Gr.:*** Hydroflux; Lasix; Semid; ***Hong Kong:*** CP-Furo; Lasix; Naqua; Urex; ***Hung.:*** Furon; Humasemide†; ***India:*** Diucontin-K; Frusemix; Frusenex; Frusix; Lasix; Petsix†; ***Indon.:*** Cetasix; Classic; Diurefo; Edemin; Farsix; Furosix; Impugan; Lasix; Uresix; ***Irl.:*** Fruside; Lasix; ***Israel:*** Fusid; Lasix†; Miphar; ***Ital.:*** Lasix; ***Malaysia:*** Dirine; Furmide†; Lasix; Rasitol; Suopinchon; Usix†; ***Mex.:*** Biomisen†; Butosali; Diurmessel; Edenol; Furomil†; Furosan; Furoter†; Henexal; Lasix; Osemin; Selectofur; Zafimida; ***Neth.:*** Lasiletten; Lasix; ***Norw.:*** Diural; Furix; Lasix; ***NZ:*** Diurin; Frusid; Lasix; ***Philipp.:*** Diuril; Diuspec; Edemann; Fremid; Fretic; Frusema; Furoscan; Fusimex; Lasix; Pharmix; Rofunil; ***Port.:*** Aqueduxt; Lasix; Naqua; ***Rus.:*** Lasix (Лазикс); ***S.Afr.:*** Aquarid; Beurises; Lasix; Puresis; Uretic; ***Singapore:*** Dirine; Furmide; Lasix; ***Spain:*** Seguril; ***Swed.:*** Furix; Impugan; Lasix; ***Switz.:*** furo-basan†; Furodrix; Furosifar†; Fursol; Impugan†; Lasix; Oedemex; ***Thai.:*** Aldic†; Dirine; Frusid†; Fudirine†; Furetic; Furide; Furine; Fuseride; H-Mide; Hawkmide†; Impugan†; Lasiven; Lasix; Mediuresix†; Urasin†; ***Turk.:*** Desal; Furomid; Lasix; Lizik; Urex; ***UAE:*** Salurin; ***UK:*** Froop; Frusid; Frusol; Lasix; Rusyde; ***USA:*** Lasix; ***Venez.:*** Biosemida; Edemid; Fromil†; Inclens; Lasix; Lifurox; Nacua†; Resimida†; Salca; Terysol.

Multi-ingredient: *Arg.:* Aldactone-D; Diflux; Errolon A; Furdiuren†; Lasilacton; Lasiride; Nuriban A; ***Austria:*** Furo-Aldopur; Furo-Spirobene; Furolacton; Hydrotrix; Lasilacton; Lasitace; Spirono comp; ***Belg.:*** Frusamil; ***Braz.:*** Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; ***Chile:*** Furdiuren; Hidrium; Hidropid; ***Cz.:*** Spiro Compositum†; ***Denm.:*** Frusamil; ***Fin.:*** Furesis comp; ***Fr.:*** Aldalix; Logirene; ***Ger.:*** Betasemid; Diaphal; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Hydrotrix; Osyrol Lasix; Spiro comp; Spiro-D; Spironolacton Plus†; ***Gr.:*** Frumil; ***India:*** Frumil; Lasilactone; Spiromide; ***Irl.:*** Diumide-K Continus; Fru-Co; Frumil; Lasoride†; ***Ital.:*** Fluss 40; Lasitone; Spirofur; ***Mex.:*** Lasilacton; ***NZ:*** Frumil; ***Philipp.:*** Diumide-K; ***Spain:*** Salidur; ***Switz.:*** Frumil†; Furocombin; Furospir; Lasilactone; ***UK:*** Aridil; Froop Co†; Fru-Co; Frumil; Frusene; Komil; Lasikal; Lasilactone; Lasoride†; ***Venez.:*** Furdiuren.

Gallopamil Hydrochloride *(BANM, rINNM)*

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydroklorid; Gallopamilli Hydrochloridum; Gallopamillihydrokloridi; Hidrocloruro de galopamilo; Methoxyverapamil Hydrochloride. 5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

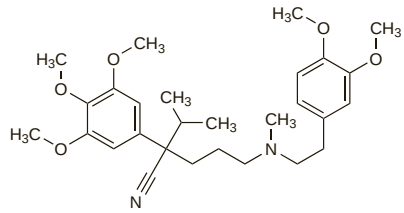
Галопамила Гидрохлорид

$C_{28}H_{40}N_2O_5,HCl$ = 521.1.

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.



(gallopamil)

Profile

Gallopamil is a calcium-channel blocker (see p.1154) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p.1157), cardiac arrhythmias (p.1160), and hypertension (p.1171). Gallopamil hydrochloride is given by mouth in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

◊ General references.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; **47:** 93–115.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Procorum; ***Ger.:*** Gallobeta; Procorum; ***Hung.:*** Procorum; ***Ital.:*** Algocor; Procorum; ***Mex.:*** Procorum; ***Philipp.:*** Procorum; ***Thai.:*** Procorum.

Gemfibrozil *(BAN, USAN, rINN)*

CI-719; Gemfibrotsiili; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl. 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

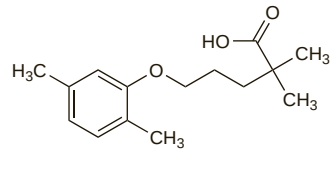
Гемфиброзил

$C_{15}H_{22}O_3$ = 250.3.

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.



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

Ph. Eur. 6.2 (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58° to 61°. Practically insoluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Gemfibrozil). A white waxy crystalline solid. M.p. 58° to 61°. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Incidence of adverse effects. In the Helsinki Heart Study,[1] 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.