



SUMMARY OF PRODUCT CHARACTERISTICS

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Furosemide Injection BP.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10mg of Furosemide BP.

3. PHARMACEUTICAL FORM

Sterile injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide is a potent diuretic with a rapid action.

It is used to treat oedema and hypertensive crises; acute or chronic renal failure.

4.2 Posology and method of administration

Furosemide is administered intravenously or intramuscularly.

Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine > 5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration are feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.

To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide infusion is generally to be preferred to repeated bolus injections. Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals

(approx. 4 hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given increasing by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly:

The dosage recommendations for adults apply, but in the elderly furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved

Children:

Parenteral doses for children range from 0.5 to 1.5 mg/kg body weight daily up to a maximum total daily dose of 20 mg

4.3 Contraindications

- Hypersensitivity to furosemide or any of the excipients. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.
- Hypovolaemia, dehydration, anuria.
- Renal failure with anuria not responding to furosemide.
- Severe hypokalaemia or hyponatraemia.
- Comatose or pre-comatose states associated with hepatic encephalopathy.
- Renal failure due to poisoning by nephrotoxic or hepatotoxic drugs.
- Renal failure associated with hepatic coma.
- Breastfeeding.

4.4 Special warnings and precautions for use

Urinary output must be secured. Patients with partial obstruction of urinary outflow have an increased risk of developing acute retention and require careful monitoring (e.g. in prostatic hypertrophy, impairment of micturition),

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy (see section 4.3 Contraindications).

Careful monitoring is required in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure.
- Patients with latent diabetes or diabetes, as furosemide may cause hyperglycaemia and increased insulin requirement.
- Patients with gout.
- Patients with hepatorenal syndrome.
- Patients with hypoproteinaemia e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- Premature infants. Furosemide may cause nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed.

Caution should be observed in patients with fluid and electrolyte imbalance. Regular monitoring of serum sodium, potassium and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

It is important to ensure that infusion rates do not exceed 4mg of Furosemide per minute. Tinnitus and deafness may occur if this rate is exceeded.

In patients who are at high risk of radiocontrast nephropathy, furosemide is not recommended for use as a diuretic as part of the preventative measures against radiocontrast-induced nephropathy.

4.5 Interactions with other medicinal products and other forms of interaction

The ototoxic and nephrotoxic effects of other medications may be increased by concomitant administration of furosemide.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain drugs (e.g. drugs inducing QT interval prolongation syndrome such as amisulpride, atomoxetine, pimozone, sotalol, sertindole).

There is increased risk of hypokalaemia when furosemide is used in combination with beta-2 sympathomimetics in large doses, theophylline, corticosteroids, liquorice, carbenoxolone, prolonged use of laxatives, reboxetine, or amphotericin.

Furosemide may sometimes attenuate the effect of other drugs e.g. the effect of anti-diabetics and of pressor amines.

Probenecid, methotrexate (see *Cytotoxic agents*) and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

Cardiac glycosides:

The potassium loss caused by potassium depleting diuretics such as furosemide increases the toxic effects of digoxin and other digitalis glycosides.

Anti-arrhythmic drugs:

Hypokalaemia caused by loop diuretics may increase the cardiac toxicity of anti-arrhythmic drugs such as amiodarone, disopyramide, flecainide, quinidine and sotalol, and may antagonise the effects of lidocaine and mexiletine.

Antihypertensive drugs:

The dosage of concurrently administered diuretics, antihypertensive agents or other drugs with blood pressure lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given with furosemide. A marked fall in blood pressure and deterioration in renal function may be seen when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists are added to furosemide therapy, or when the dosage is increased. The dose of furosemide should be reduced for at least three days, or the drug stopped before initiation of ACE-inhibitor or angiotensin II receptor antagonist therapy, or before their dose is increased.

Lithium:

In common with other diuretics, serum lithium levels may be increased when furosemide is given to patients stabilised on this therapy, resulting in increased lithium toxicity (cardiotoxicity, neurotoxicity). It is recommended that lithium levels are carefully monitored and where necessary the lithium dosage adjusted during concurrent use.

Non-steroidal anti-inflammatory drugs:

Certain NSAIDs (including indometacin, ketorolac, acetylsalicylic acid) may decrease the effectiveness of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylate toxicity may be increased by furosemide.

Antibiotics:

Furosemide may potentiate the nephrotoxicity and ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with furosemide when there are compelling medical reasons.

There is an increased risk of ototoxicity when loop diuretics are given with vancomycin or polymyxins (colistin).

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins (e.g. cephaloridine).

Cytotoxic agents:

There is a risk of ototoxicity if cisplatin and furosemide are given concurrently. Low doses of furosemide (e.g. 40 mg in patients with normal renal function) should be used and a positive fluid balance maintained when furosemide is used to achieve forced diuresis during cisplatin treatment to reduce the risk of additional nephrotoxicity.

Methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of methotrexate. This may lead to increased serum levels and increased risk of adverse events, especially with high dose therapy of methotrexate or furosemide.

Ciclosporin:

Concomitant use of ciclosporin and furosemide is associated with an increased risk of gouty arthritis.

Anti-convulsants:

Phenytoin may decrease the effectiveness of furosemide. Concomitant administration of carbamazepine may increase the risk of hyponatraemia.

Corticosteroids:

Concurrent use of corticosteroids may cause sodium retention and increased risk of developing hypokalaemia.

Chloral hydrate/Triclofos:

Bolus doses of intravenous furosemide may induce flushing, sweating, tachycardia and variations in blood pressure in patients receiving chloral hydrate or triclofos.

Neuromuscular blocking agents:

Furosemide may affect the response to neuromuscular blocking agents (increased or decreased effect).

4.6 Pregnancy and lactation

Pregnancy:

Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, furosemide crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Lactation:

Furosemide passes into breast milk and may inhibit lactation. Women must not breast-feed if they are treated with furosemide.

4.7 Effects on ability to drive and use machines

Reduced mental alertness may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects

The most common undesirable effect is fluid and electrolyte imbalance. Other undesirable effects are relatively uncommon.

Blood and lymphatic system disorders:

Eosinophilia is rare. Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Immune system disorders:

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low, but when these occur treatment should be withdrawn.

Metabolism and nutrition disorders:

Electrolyte and water balance may be disturbed as a result of diuresis. Furosemide causes increased excretion of sodium and chloride and consequently water, and hyponatraemia may occur. The diuretic action of furosemide may lead to or contribute towards hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

Excretion of other electrolytes is increased, and hypokalaemia, serum calcium depletion and hypomagnesaemia may occur. Symptomatic electrolyte disturbances and metabolic alkalosis may develop following gradual electrolyte depletion or acute severe electrolyte losses during higher dose therapy. Warning signs of electrolyte disturbances include increased thirst, headache, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long-term therapy they will usually return to normal within six months.

Furosemide may provoke hyperglycaemia and glycosuria but less so than thiazide diuretics. Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus, this may lead to a deterioration of control; latent diabetes mellitus may become manifest.

Furosemide can increase serum uric acid levels and may precipitate attacks of gout in some patients.

Psychiatric/Nervous system disorders:

Rarely paraesthesia may occur. Symptoms of hypotension may include dizziness, light-headedness, sensation of pressure in the head, headache, drowsiness, concentration impairment and slowed reactions. Headache, lethargy or confusion may be warning signs of electrolyte disturbances.

Eye disorders:

Visual disturbances, blurred vision.

Ear and labyrinth disorders:

Hearing disorders, including deafness and tinnitus, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. nephrotic syndrome) and/ or when intravenous furosemide has been given too rapidly. Although symptoms are usually transient, permanent deafness may occur, especially in patients treated with other ototoxic medications (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions)

Cardiac disorders:

Cardiac rhythm disturbances may occur as a consequence of electrolyte imbalance.

If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Vascular disorders:

Hypotension and orthostatic hypotension may occur, especially in patients taking other medications which lower blood pressure. Allergic vasculitis has been reported very rarely.

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea and dry mouth may occur but are not usually severe enough to necessitate withdrawal of treatment.

Hepatobiliary disorders:

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Skin and subcutaneous tissue disorders:

Skin and mucous membrane reactions may occasionally occur eg pruritis, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis and purpura.

Musculoskeletal disorders:

Serum calcium levels may be reduced, muscle spasms or muscle weakness may indicate electrolyte disturbances. In very rare cases tetany has been observed.

Renal and urinary disorders:

Treatment with furosemide may lead to transient increases in blood creatinine and urea levels. Renal failure may occur as a consequence of fluid and electrolyte depletion, especially during concurrent treatment with NSAIDs or nephrotoxic medications.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Acute retention of urine with possible secondary complications may occur, for example, in patients with bladder emptying disorders, prostatic hyperplasia or narrowing of the urethra (see section 4.4 Special warnings and precautions for use).

Nephrocalcinosis/nephrolithiasis has been reported in premature infants, and in adults, generally after long-term therapy.

There have been very rare reports of interstitial nephritis.

General disorders:

Asthenia, malaise, fever.

Following intramuscular injection, local reactions such as pain may occur.

4.9 Overdose

Symptoms:

Hypovolaemia, dehydration, haemoconcentration, hyponatraemia, and hypokalaemia may occur following overdose of furosemide injection. Severe hypotension, progressing to shock, cardiac arrhythmias, acute renal failure, thrombosis, delirium, flaccid paralysis, apathy and confusion may occur as a result of electrolyte and fluid loss,

Management:

No specific antidote to furosemide injection is known. Furosemide should be withdrawn or the dose reduced. Treatment should be supportive and aimed at fluid replacement, correction of electrolyte imbalance and maintenance of blood pressure.

Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Furosemide is a potent diuretic. It is an anthranilic acid derivative and chemically it is 4-chloro-Nfurfuryl-5sulpha-moylanthranilic acid. Furosemide inhibits the reabsorption of sodium and chloride in the loop of Henle as well as in the proximal and distal tubules; its action is independent of any inhibitory effect on carbonic anhydrase. The urinary excretion of potassium, calcium and magnesium is increased by Furosemide. Hyperuricaemia may occur and is presumed to result from a competitive inhibition of urate secretion in the proximal tubules.

Furosemide has a steep dose-response curve and is designated a high-ceiling diuretic. Following intravenous administration, the onset of diuresis is within 5 minutes and the duration of diuretic effect is approximately two hours.

5.2 Pharmacokinetic properties

Furosemide is extensively bound to plasma proteins and is mainly excreted in the urine, largely unchanged. Significantly more Furosemide is excreted in urine following intravenous injection than after the tablet form. Furosemide glucuronide is the main biotransformation product.

Furosemide has a biphasic half-life in plasma with a terminal elimination phase of approximately 1.5 hours. Although mainly excreted in the urine, variable amounts are also excreted in bile and non-renal elimination may be considerably increased in renal failure.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride Ph. Eur.
Sodium Hydroxide BP.
Water for Injections Ph. Eur.

6.2 Incompatibilities

Furosemide should not be mixed with any other medication in the same syringe e.g. Furosemide produces a precipitate when mixed with Dobutamine, Diazepam, Doxorubicin, Droperidol, Gentamicin, Glucose, Mannitol, Metoclopramide, Potassium Chloride, Tetracycline, Vincristine and Vitamins.

It should not be given during infusion with Adrenaline, Isoprenaline, Lidocaine or Pethidine.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store below 25° C and protect from light.

6.5 Nature and contents of container

2, 5 and 25ml type I amber glass ampoules, packed in cardboard cartons to contain 10 ampoules.

6.6 Instructions for use, handling and disposal

Use as directed by the physician.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

hameln pharmaceuticals ltd
Gloucester
UK

8. MARKETING AUTHORISATION NUMBER

PL 1502/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

23rd September 1997

10. DATE OF (PARTIAL) REVISION OF TEXT

19/08/08