SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 10 mg/ml solution for injection

2.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 mg furosemide (10 mg/ml).
Each 2 ml of solution contains 20 mg furosemide (10 mg/ml).
Each 4 ml of solution contains 40 mg furosemide (10 mg/ml).
Each 5 ml of solution contains 50 mg furosemide (10 mg/ml).
Each 25 ml of solution contains 250 mg furosemide (10 mg/ml).

Excipient(s) with know effect:
This medicinal product contains a maximum 4 mg sodium per 1 ml of solution.

For the full list of excipients, see section 6.1.

3 PHARMACETICAL FORM

Solution for injection.

Furosemide 10 mg/ml solution for injection is clear colourless to slightly brownish yellow solution, free from visible particles.
pH 8.0-9.3

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide 10 mg/ml solution for injection is a diuretic indicated for use when a prompt and effective diuresis is required. The intravenous formulation is appropriate for use in emergencies or when oral therapy is precluded. Indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and method of administration

Posology

Adults

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.

Paediatric population
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.

Method of administration
Furosemide 10 mg/ml solution for injection 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.

For instruction on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Patients allergic to sulfonamides or sulfonamide derivatives may show cross-sensitivity to furosemide. Hypersensitivity to amiloride.
- 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.
- Impaired renal function with a creatinine clearance below 30 ml/min per 1.73m^2 body surface area (see section 4.4).
- Addison's disease (see section 4.4).
- Porphyria.
- Digitalis intoxication (see section 4.5).
- Breast-feeding (see section 4.6).

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 or lower dose should be considered (e.g. in prostatic hypertrophy, impairment of micturition).

Where indicated, steps should be taken to correct hypotension, hypovolaemia and severe electrolyte disturbances – particularly hypokalaemia, hyponatremia and acid-base disturbances before commencing therapy (see section 4.3).

Particular caution and/or dose reduction required
Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Careful monitoring is required in
- Patients with latent diabetes or diabetes, as furosemide may cause hyperglycaemia and increased insulin requirement (furosemide should be stopped before a glucose tolerance test).
- Patients with gout.
- Patients with hepatorenal syndrome.
- Patients with hypoproteinaemia e.g. associated with nephritic 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.
- Patients experiencing difficulties with micturition including prostatic hypertrophy (increased risk of urinary retention: lower dose should be considered) and with partial occlusion of the urinary tract.
- Pregnancy.
- Impaired hepatic function.

- Impaired renal function.
- Adrenal disease (see section 4.3 contraindicated in Addison's disease).

It is important to ensure that infusion rates do not exceed 4 mg of Furosemide 10 mg/ml solution for injection 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.

Laboratory monitoring requirements

Serum sodium and potassium
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, in case of significant additional fluid loss and in older people. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

The possibility of hypokalaemia should be taken into account, in particular in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an unbalanced diet and those who abuse laxatives. Regular monitoring of potassium, and if necessary treatment with a potassium supplement, is recommended in all cases, but is essential at higher doses and in patients with impaired renal function. It is especially important in the event of concomitant treatment with digoxin, as potassium deficiency can trigger or exacerbate the symptoms of digitalis intoxication (see section 4.5). A potassium-rich diet is recommended during long-term use.

Frequent checks of the serum potassium are necessary in patients with impaired renal function and creatinine clearance below 60 ml/min per 1.73m^2 body surface area as well as in cases where furosemide is taken in combination with certain other drugs which may lead to an increase in potassium levels (see section 4.5 and 4.8 for details of electrolyte and metabolic abnormalities).

Renal function
Blood urea nitrogen (BUN) should be frequently measured in the first few months of treatment, periodically thereafter. BUN should be regularly measured if long-term/high-dose furosemide treatment is required. Marked diuresis can cause reversible impairment of kidney function in patients with renal dysfunction. Adequate fluid intake is necessary in such patients. Serum creatinine and urea levels tend to rise during treatment.

Glucose
Adverse effect on carbohydrate metabolism-exacerbation of existing glucose intolerance or diabetes mellitus. Regular monitoring of blood glucose levels is desirable.

Other electrolytes

Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesemia (as well as hypokalaemia). During long-term therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

Clinical monitoring requirements

Regular monitoring for:

- Blood dyscrasias. If these occur, furosemide should be stopped immediately.
- Liver damage
- Idiosyncratic reactions

Other alterations in lab values

Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide.

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

Concomitant use with NSAIDs

Concurrent use of NSAIDs and furosemide should be avoided if possible. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics. Use of NSAIDs with diuretics may increase the risk of nephrotoxicity.

Concomitant use with risperidone

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3).

Furosemide 10 mg/ml solution for injection contains sodium

This medicinal product contains a maximum 4 mg sodium per 1 ml of solution.

This medicinal product contains a maximum 100 mg sodium per 25 ml of solution, equivalent to 5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction 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. cardiac glycosides, drugs inducing QT interval prolongation syndrome such as amisulpride, atomoxetine, pimozide, sotalol, sertindole) and increase the risk of ventricular arrhythmias.

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, tocainide 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.

- *ACE-inhibitors and angiotensin II receptor antagonists:*

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.

- *Vasodilators:*

Furosemide enhances the hypotensive effect of vasodilators such as moxisylyte (thymoxamine) or hydralazine.

- *Renin Inhibitors:*

Plasma concentration of furosemide may be reduced by aliskiren.

- *Xanthines:*

Concomitant use of theophylline is associated with increased risk of enhanced hypotensive effect.

- *Nitrates:*

Hypotensive effect may be enhanced when furosemide is given with nitrates.

- *Other diuretics:*

Profound diuresis is possible when furosemide is given with metolazone. There is an increased risk of hypokalaemia when furosemide is given with thiazides.

Antidiabetic:
Furosemide as a loop diuretic antagonises the hypoglycaemic effect of antidiabetics. The blood levels of metformin may be increased by furosemide. Inversely, metformin may reduce furosemide concentration. The risk is linked to an increased occurrence of lactic acidosis in case of functional renal insufficiency.

Antipsychotics:
Concomitant use with pimozide should be avoided (increased risk of ventricular arrhythmias due to furosemide-induced hypokalaemia). A similar effect is observed with amisulpride and sertindole. The hypotensive effect is enhanced when furosemide is concomitantly used with phenothiazines.

When administering risperidone, caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. See section 4.4 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Antidepressants:
There is an increased risk of postural hypotension when furosemide is given with tricyclic antidepressants (TCAs) and an enhanced hypotensive effect with monoamine-oxidase inhibitors (MAOIs). Concomitant use with reboxetine may increase the risk of hypokalaemia.

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 (see section 4.4).

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). Furosemide can decrease vancomycin serum levels after cardiac surgery.

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

There is an increased risk of hyponatraemia with trimethoprim.

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.

Immunomodulators:
Concomitant use of cyclosporine and furosemide is associated with an increased risk of gouty arthritis. Hypotensive effect of furosemide may be enhanced when given with aldesleukin.

Antihistamines:
Hypokalaemia with increased risk of cardiac toxicity.

Anti-convulsants:
Phenytoin may decrease the effectiveness of furosemide. Concomitant administration of carbamazepine may increase the risk of hyponatraemia.

Dopaminergics:
There is an enhanced hypotensive effect when furosemide is given concomitantly with levodopa.

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. Administration of parenteral furosemide with chloral hydrate may displace thyroid hormone from binding sites.

Muscle relaxants:
Hypotensive effect of furosemide may be enhanced when given with baclofen or tizanidine.

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

Anaesthetic agents:
General anaesthetic agents may enhance the hypotensive effects of furosemide.

Oestrogens:
Diuretic effect of furosemide may be antagonised by oestrogens.

Prostaglandins:
Hypotensive effect of furosemide may be enhanced when given with alprostadil.

Alcohol:
Enhanced hypotensive effect when used concomitantly with furosemide.

Others:
Concomitant administration of aminoglutethimide may increase the risk of hyponatraemia.

4.6 Fertility, 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 fetal growth.

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

Fertility
No data available

4.7 Effects on ability to drive and use machines

Furosemide 10 mg/ml solution for injection has negligible influence on the ability to drive and use machinery.
Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised not to drive or operate machinery or take part in activities where these effects could put themselves or others at risk if they are affected.

4.8 Undesirable effects

Undesirable effects can occur with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000, including isolated reports), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Uncommon: thrombocytopenia.
Rare: eosinophilia, leukopenia, bone marrow depression which necessitates withdrawal of treatment. The hematopoietic status should be therefore regularly monitored.
Very rare: agranulocytosis, aplastic anaemia, haemolytic anaemia.

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 administered to patients with normal renal function.
Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

Warning signs of electrolyte disturbances depend on the type of disturbances.
Sodium deficiency can manifest itself as: confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.
Potassium deficiency can manifest itself as: muscular weakness, paralysis, gastrointestinal symptoms (vomiting, constipation and meteorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.
Magnesium and calcium deficiency result very rarely in tetany and heart rate disturbances.

Metabolic acidosis can also occur. The risk of this abnormality increases at higher doses and is influenced by the underlying disorder (e.g. liver cirrhosis, heart failure), concomitant medications (see section 4.5) and diet.

Serum cholesterol (reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol) and triglyceride levels may rise during furosemide treatment. During long-term therapy they will usually return to normal within six months.

As with other diuretics, treatment with furosemide may lead to transitory increase in blood creatinine and urea levels. Furosemide may increase the levels of uric acid and precipitate gout.

Endocrine disorders:
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 and insulin requirements of diabetic patients may increase (see section 4.4).

Psychiatric/Nervous system disorders:
Rarely paraesthesia and hyperosmolar coma may occur.
Not known: dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).
Symptoms of hypotension may also 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:
Uncommon: 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. nephritic syndrome) and/or when intravenous furosemide has been given too rapidly. Although symptoms are usually transient, deafness (sometimes irreversible) (uncommon) may occur, especially in patients treated with other ototoxic medications (see section 4.4 and section 4.5).

Cardiac disorders:
Cardiac rhythm disturbances (uncommon) 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, constipation, dry mouth, thirst, bowel motility disturbances are uncommon 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 (rare) may develop.

Skin and subcutaneous tissue disorders:
Uncommon: photosensitivity
Rare: skin and mucous membrane reactions may occasionally occur eg pruritis, urticaria, other rashes or bullous lesions, hypersensitivity to light, erythema multiforme, bullous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's Syndrome), exfoliative dermatitis, purpura, acute generalised exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal and connective tissue 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 (uncommon). Renal failure may occur (rarely) 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).

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

There have been rare reports of interstitial nephritis.

General disorders and administration site conditions:
Uncommon: asthenia.
Rare: malaise, fever.

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

Pregnancy, puerperium and perinatal conditions:
In premature infants with respiratory distress syndrome, administration of furosemide during the first weeks of life may increase the risk of persistence of patent ductus arteriosus.

In premature infants, furosemide can be precipitated as nephrocalcinosis/ kidney stones.

Rare complications may include minor psychiatric disturbances.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Hypovolaemia, dehydration, haemoconcentration, hyponatraemia, and hypokalaemia may occur following overdose of furosemide.

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.

High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Management
No specific antidote to furosemide 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

Pharmacotherapeutic group: Diuretics; Sulfonamides, plain, ATC code: C03CA01

Mechanism of action
Furosemide is a potent diuretic. It is an anthranilic acid derivative and chemically it is 4-chloro-Nfurfuryl-5sulfa-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.

Pharmacodynamic effects
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

Distribution
Furosemide is extensively bound to plasma proteins and is mainly excreted in the urine, largely unchanged.

Biotransformation
Furosemide glucuronide is the main biotransformation product.

Elimination
Significantly more furosemide is excreted in urine following intravenous injection than after the tablet form. 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.

In renal/hepatic impairment:
Where liver disease is present, biliary elimination is reduced up to 50%. Renal impairment has little effect on the elimination rate of furosemide, but less than 20% residual renal function increases the elimination time.

The elderly:
The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

Neonates:
A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function

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
Sodium hydroxide (for pH-adjustment)
Water for injections

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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoules: 3 years.

Opened ampoules: The product should be used immediately after opening the container.

Prepared infusion solutions:
Chemical and physical in-use stability has been demonstrated in glucose solution 50 mg/ml (5%), sodium chloride solution 9 mg/ml (0.9%) and Ringer solution for 72 hours at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25 °C. Store in the original package in order to protect from light.
For storage conditions after first opening or dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Furosemide 10 mg/ml solution for injection is supplied in 2 ml, 5 ml and 25 ml amber glass ampoules type I with one point cut (OPC), containing 2 ml, 4 ml, 5 ml or 25 ml solution for injection.

The following pack sizes are available for Furosemide 10 mg/ml solution for injection:
5 or 10 ampoules in cartons contents 2 ml solution
5 or 10 ampoules in cartons contents 4 ml solution
5 or 10 ampoules in cartons contents 5 ml solution
5 or 10 ampoules in cartons contents 25 ml solution
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Furosemide 10 mg/ml solution for injection can be diluted with glucose 50 mg/ml (5%), sodium chloride 9 mg/ml (0.9%) or Ringer solution.
The drug product should be examined visually and should not be used if particulate matter or discolouration are present.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/00129

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/05/2018

10 DATE OF REVISION OF THE TEXT

24/01/2024