SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide Injection 10mg/ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains furosemide BP 10mg.
For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Liquid for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diuretic. Oedema of cardiac, hepatic or renal origin, pulmonary oedema, toxaemia of pregnancy, and mild or moderate hypertension, toxaemia of pregnancy

4.8 Undesirable effects

Adverse reactions reported for furosemide are given below according to organ systems. The frequencies of the adverse reactions are classified as follows: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 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):

System Organ	Adverse Drug Reactions- Frequency Category

Class	Uncommon (≥ 1/1000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders	Thrombocytopenia	Eosinophilia Leucopenia Bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should be regularly monitored.	Aplastic anaemia Haemolytic anaemia Agranulocytosis	
Immune system disorders		Severe anaphylactic or anaphylactoid reactions (e.g. with shock)		

Nervous system disorders		Paraesthesia Hyperosmolar coma		Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)
Endocrine disorders				Decrease in glucose tolerance[4]
Eye disorders	Visual disturbance			
Ear and labyrinth disorders	Deafness (sometimes irreversible)	Hearing disorders Tinnitus		
Cardiac disorders	Cardiac arrhythmias			Reduction in blood pressure Disorders of cardiac rhythm Impairment of concentration and reactions Light-headedness Sensations of pressure in the

				head Headache Dizziness Drowsiness Weakness Disorders of vision Dry mouth Orthostatic intolerance
Hepatobiliary disorders				Intrahepatic cholestasis Increase in liver transaminases Acute pancreatitis Hepatic encephalopathy
Vascular disorders		Vasculitis		

Skin and subcutaneous tissue disorders	Photosensitivity	Itching Urticaria Other rashes or bullous lesions Fever Hypersensitivity to light Exsudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome) Bullous exanthema Exfoliative dermatitis Purpura DRESS (Drug rash with eosinophilia and systemic symptoms)		AGEP (acute generalised exanthematous pustulosis)
Metabolism and nutrition disorders:				Electrolyte and water imbalance[1] Hyponatraemia Hypokalaemia Hypochloraemia Hypomagnesaemia Metabolic alkalosis Metabolic acidosis

				Hypovolaemia[2] cholesterol and triglyceride levels[3] Decrease in glucose tolerance[4] Hyperuricaemia Gout
Congenital, familial and genetic disorders				Persistence of patent ductus arteriosus (in premature infants)
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Dry mouth Thirst Bowel motility disturbances Constipation	Acute pancreatitis		

Musculoskeletal and connective tissue disorders			Tetany	Muscle cramps Muscle weakness Hypocalcaemia
Renal and urinary disorders	Increase in serum creatinine and urea levels	Increased production of urine Nephrocalcinosis / Nephrolithiasis (in premature infants) Interstitial nephritis Acute renal failure		
General disorders and administration site conditions	Fatigue	Severe anaphylactic or anaphylactoid reactions (e.g. with shock) Fever Malaise		
Pregnancy				In premature infants with respiratory distress syndrome, administration of Furosemide in the initial weeks after birth entails an increased risk of a persistent patent ductus

Additional information

[1] Electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to

patients with normal renal function, acute severe electrolyte losses.

[2] Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

[3] During long term therapy they will usually return to normal within six months.

[4] In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

Insulin requirements of diabetic patients may increase.

Paediatric population

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

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

Other special

populations

Elderly

patients

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients.

Patients with hepatic impairment

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

Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

Patients with renal impairment

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in

section 6.1

Hypersensitivity to amiloride, sulphonamides or sulphonamide derivatives

Hypovolaemia and dehydration (with or without accompanying hypotension) (see section 4.4)

Severe hypokalaemia, severe hyponatraemia (see section 4.4).

Comatose or pre-comatose states associated with hepatic cirrhosis (see section 4.4)

Anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents, renal failure associated with hepatic coma

Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m2 body surface area (see section 4.4)

Addison's disease (see section 4.4)

Digitalis intoxication (see section 4.5)

Porphyria

Breast-feeding women (see section 4.6)

4.4 Special warnings and precautions for use

Conditions requiring correction before furosemide is started (see also section 4.3)

• Hypotension.

• Hypovolaemia.

• Severe electrolyte disturbances – particularly hypokalaemia, hyponatraemia and acid-base disturbances.

Furosemide is not recommended

• In patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

• In patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

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.

• Older people (lower initial dose as particularly susceptible to side-effects – see section 4.2)

• Difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract

• Diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test)

• Pregnancy (see section 4.6)

• Gout (furosemide may raise uric acid levels/precipitate gout)

• Patients with hepatorenal syndrome

• Impaired hepatic function (see section 4.3 and below – monitoring required)

• Impaired renal function (see section 4.3 and below – monitoring required)

• Adrenal disease (see section 4.3 – contraindication in Addison's disease)

• Hypoproteinaemia e.g. nephritic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated - cautious dose titration required).

• Acute hypercalcaemia (dehydration results from vomiting and diuresis – correct before giving furosemide). Treatment of hypercalcaemia with a high dose of furosemide results in fluid and electrolyte depletion - meticulous fluid replacement and correction of electrolyte required.

• Patients who are at risk from a pronounced fall in blood pressure

• Premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

Avoidance with other medicines (see also section 4.5 for other interactions)

• concurrent NSAIDs should be avoided – if not possible diuretic effect of furosemide may be attenuated

• ACE-inhibitors & Angiotensin II receptor antagonists – severe hypotension may occur – dose of furosemide should be reduced/stopped (3 days) before starting or increasing the dose of these

Laboratory monitoring requirements:
• Serum sodium

Particularly in the older people or in patients liable to electrolyte deficiency

• Serum potassium

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 the 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 60ml/min per 1.73m2 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 & refer to section 4.8 for details of electrolyte and metabolic abnormalities)

• Renal function

Frequent BUN in first few months of treatment, periodically thereafter. Long term/high-dose BUN should regularly be measured. 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 carbohydrate 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 hypomagnesia (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 (see also section 4.8):

Regular monitoring for

• blood dyscrasias. If these occur, stop furosemide 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

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 Contraindications).

4.5 Interaction with other medicinal products and other forms of interaction

General: The dosage of concurrently administered cardiac glycosides, 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 concomitantly with Furosemide.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration with potent diuretics such as furosemide.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

Antihypertensives: Enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, furosemide should be stopped or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists (see section 4.4)

Antipsychotics: furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect 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.

Anti-arrhythmics (including amiodarone, disopyramide, flecanaide and sotalol): risk of cardiac toxicity (because of furosemide-induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Cardiac glycosides: hypokalaemia and electrolyte disturbances (including hypomagnesia) increase the risk of cardiac toxicity.

Drugs that prolong Q-T interval: increased risk of toxicity with furosemide-induced electrolyte disturbances

Vasodilators: enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine

Other diuretics: profound diures is possible when furosemide given with metolazone.

Increased risk of hypokalaemia with thiazides.

Renin inhibitors: aliskiren reduces plasma concentrations of furosemide

Nitrates: enhanced hypotensive effect

Lithium: In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Chelating agents: sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart

NSAIDs: increased risk of nephrotoxicity. Indometacin and ketorolac may antagonise the effects of furosemide (avoid if possible see section 4.4). NSAIDs may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.

Salicylates: effects may be potentiated by furosemide. Salycylic toxicity may be increased by furosemide

Antibiotics: increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatraemia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Antidepressants: enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalaemia with reboxetine

Antidiabetics: hypoglycaemic effects antagonised by furosemide

Antiepileptics: increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antihistamines: hypokalaemia with increased risk of cardiac toxicity

Antifungals: increased risk of hypokalaemia and nephrotoxicity with amphotericin

Anxiolytics and hypnotics: enhanced hypotensive effect. Chloral or triclorfos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD): hypokalaemia increases the risk of ventricular arrhythmias

Corticosteroids: diuretic effect anatgonised (sodium retention) and increased risk of hypokalaemia

Glychyrrizin: (contained in liquorice) may and increase the risk of developing hypokalaemia.
Cytotoxics: increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. Nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Anti-metabolites: effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate

Dopaminergics: enhanced hypotensive effect with levodopa.

Immunomodulators: enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosprin and tacrolimus. Increased risk of gouty arthritis with ciclosporin

Muscle relaxants: enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants

Oestrogens: diuretic effect antagonised

Progestogens (drosperidone): increased risk of hyperkalaemia

Prostaglandins: enhanced hypotensive effect with alprostadil

Sympathomimetics: increased risk of hypokalaemia with high doses of beta2 sympathomimetics

Theophylline: enhanced hypotensive effect

Probenecid: effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.

Anaesthetic agents: general anaesthetic agents may enhance the

hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

Alcohol: enhanced hypotensive effect

Laxative abuse: increases the risk of potassium loss

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Furosemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons. It should only be used for the pathological causes of oedema which are not directly or indirectly linked to the pregnancy. The treatment with diuretics of oedema and hypertension caused by pregnancy is undesirable because placental perfusion can be reduced, so, if used, monitoring of fetal growth is required. However,
furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxaemia of pregnancy without causing fetal or newborn adverse effects.

Breast-feeding (see section 4.3)

Furosemide is contraindicated as it passes into breast milk and may inhibit lactation.

4.7 Effects on ability to drive and use machines

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 that if affected, they should not drive, operate machinery or take part in activities where these effects could put themselves or others at risk.

4.2 Posology and method of administration

Furosemide Injection may be used when oral application of furosemide is precluded or in cases of emergency.

Adults:

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 (approximately four 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 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.

Children: Parenteral doses for children range from 0.5mg to 1.5mg per kilogram body weight daily up to a maximum total daily dose of 20mg.

Elderly:

In the elderly furosemide is generally eliminated more slowly. Dosage should be adjusted according to the observed clinical response.

Method of administration: by intravenous infusion or intramuscular injection.

4.9 Overdose

Symptoms:

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment:

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. 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.

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of

the active ingredient by measures such as those designated to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diuretics, ATC code: C03CA01

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henle with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex. The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and a hypotonic or isotonic urine produced. It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is bound to plasma albumin and little biotransformation takes place. Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

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 Injection, 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.

New born

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

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide and water for injections.

6.2 Incompatibilities

Not known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place. Protect from light.

6.5 Nature and contents of container

Sterile amber glass ampoules.
2ml in packs of 10 and 25.
5ml in packs of 5.

6.6 Special precautions for disposal

Furosemide Injection should not be mixed with any other preparation.

Opened ampoules should be used immediately, and any material remaining should be discarded.

7 MARKETING AUTHORISATION HOLDER

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