# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Furosemide Pfizer 10mg/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution contains 10mg furosemide.
Each 2 ml ampoule contains 20 mg of furosemide (20 mg/2 ml)
Each 5 ml ampoule contains 50 mg of furosemide (50 mg/5 ml)

Excipients Sodium 0.3mmol per 2ml.

For a full list of excipients, see section 6

## 3 PHARMACEUTICAL FORM

Solution for injection.
A clear and colourless solution, essentially free from visible particles.
pH of the solution is between 8.00 and 9.30.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

When a prompt diuresis is required. Use in emergencies or when oral therapy is precluded. Indications include:
- *Oedema and/or ascites caused by cardiac or hepatic diseases*
- *Oedema caused by renal diseases (in case of nephrotic syndrome, treatment of the underlying disease is essential)*
- *Pulmonary oedema (e.g. in case of acute heart failure)*
- *Hypertensive crisis (in addition to other therapeutic measures)*

### 4.2 Posology and method of administration

Route of administration: intravenous or (in exceptional cases) intramuscular

General:
The parenteral administration of furosemide is indicated in cases where oral administration is not feasible or not efficient (for example in case of reduced intestinal absorption) or when a quick effect is required. 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.
Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response.

Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded and should never be given in association with other medicinal products in the same syringe.

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

Adults:
In the absence of conditions requiring a reduced dose (see below) the initial dose recommended for adults and adolescents over 15 years, is of 20 mg to 40 mg furosemide (1 or 2 ampoules) by intravenous (or in exceptional cases intramuscular) administration; the maximum dose varying according to individual response.

If larger doses are required, they should be given increasing by 20 mg increments and not given more often than every two hours.
In adults, the recommended maximum daily dose of furosemide administration is 1500 mg.

The parenteral administration of furosemide is indicated in cases where oral administration is not feasible or not efficient (for example in case of reduced intestinal absorption) or when a quick effect is required. **In cases where parenteral administration is used, the switch to oral administration is recommended, as soon as possible.**

Children and adolescents (up to 18 years of age):
The experience in children and adolescents are limited. The intravenous administration of furosemide to children and adolescents below 15 years is only recommended in exceptional cases.
The dosage will be adapted to the body weight, and the recommended dose ranges from 0.5 to 1 mg/kg body weight daily up to a maximum total daily dose of 20 mg.
There should be a switch to oral therapy as soon as possible.

Renal impairment:
In patients with severe impairment of renal function (serum creatinine > 5 mg/dl) it is recommended that an infusion rate of 2.5 mg furosemide per minute is not exceeded.

Elderly:
The recommended initial dose is 20 mg/day, increasing gradually until the required response is achieved.

<u>Special dosage recommendations:</u>
For adults, the dose is based on the following conditions:

- Oedema associated to chronic and acute congestive heart failure

The recommended initial dose is 20 to 40 mg daily. This dose can be adapted to the patient´s response, as necessary. The dose should be given in two or three individual doses per day for chronic congestive heart failure and as a bolus for acute congestive heart failure.

- Oedema associated with renal disease

The recommended initial dose is 20 to 40 mg daily. This dose can be adapted to the response as necessary. The total daily dose can be administered as a single dose or as several doses throughout the day.
If this does not lead to an optimal fluid excretion increase, furosemide must be administered in continuous intravenous infusion, with an initial rate of 50 mg to 100 mg per hour.
Before beginning the administration of furosemide, hypovolaemia, hypotension and acid-base and electrolytic imbalances must be corrected.
In dialyzed patients, the usual maintenance dose ranges from 250 mg to 1,500 mg daily.
In patients with nephrotic syndrome the dosage must be determined with caution, because of the risk of a higher incidence of adverse events.

- Oedema associated with hepatic disease

When intravenous treatment is absolutely needed, the initial dose should range from 20 mg to 40 mg. This dose can be adapted to the response as necessary. The total daily dose can be administered as a single dose or in several doses.
Furosemide can be used in combination with aldosterone antagonists in cases in which these agents in monotherapy are not sufficient. In order to avoid complications such as orthostatic intolerance or acid-base and electrolytic imbalances or hepatic encephalopathy, the dose must be carefully adjusted to achieve a gradual fluid loss. The dose may produce in adults a daily body weight loss of approximately 0.5 kg.
In cases of ascites with oedema, weight loss induced by enhanced diuresis should not exceed 1 kg / day.

- Pulmonary oedema (in acute heart failure)
The initial dose to be administered is 40 mg furosemide by intravenous application. If required by the condition of the patient, another injection of 20 to 40 mg furosemide is given after 30 – 60 minutes.
Furosemide should be used in addition to other therapeutic measures.

- Hypertensive crisis (in addition to other therapeutic measures)
The recommended initial dose in hypertensive crisis is 20 mg to 40 mg administrated in bolus by intravenous injection. This dose can be adapted to the response as necessary.

## 4.3 Contraindications

- Hypersensitivity to the active substance ” furosemide” or to any of the excipients.
– Patients with anuria or renal failure with oligoanuria not responding to furosemide
– Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents
– Renal failure associated with hepatic coma
– Patients with severe hypokalaemia or severe hyponatraemia
– Patients with hypovolaemia (with or without hypotension) or dehydration
– Patients in pre-comatose and comatose state associated with hepatic encephalopathy
– Patients with hypersensitivity to sulphonamides (e.g. Sulfonyureas or antibiotics of sulphonamides group) may show cross-sensitivity to furosemide
– Lactation (see section 4.6)

## 4.4 Special warnings and precautions for use

Careful monitoring is required in case of:
- Patients with partial obstruction of urinary outflow (e.g. prostatic hypertrophy, hydronephrosis, ureterostenosis). Urinary output must be secured
- Patients with hypotension or at increased risk from pronounced fall in blood pressure (patients with coronary artery stenosis or cerebral artery stenosis)
- Patients with manifest or latent diabetes mellitus or variation of glycaemia (regular monitoring of blood glucose levels necessary)
- Patients with gout and hyperuricaemia (regular monitoring of uric acid levels in serum necessary)
- Patients with hepatic disease or hepatorenal syndrome (renal impairment associated to severe hepatic disease)
- Hypoproteinaemia (associated to nephrotic syndrome, furosemide´s effect may be reduced and its ototoxicity increased)
- Co-administration with lithium salts (monitoring of lithium levels is required, see section 4.5)
- Acute porphyria (the use of diuretics is considered to be unsafe in acute porphyria and caution should be exercised)
- In cases of ascites with oedema, weight loss induced by enhanced diuresis should not exceed 1 kg / day
- Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes.
- NSAIDs may antagonise the diuretic effect of furosemide and other diuretics. Use of NSAIDs with diuretics may increase the risk of nephrotoxicity.
- Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Cautious dose titration is required:
- Electrolyte variations (e.g. hypokalaemia, hyponatraemia). Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia
- Fluid variations, dehydration, blood volume reduction with circulatory collapse and possibility of thrombosis and embolism, particular in elderly, with excessive use
- Ototoxicity (if administered faster than 4 mg/min - other ototoxic compounds administered concomitantly can increase this risk, see section 4.5
- Administration of high dosages
- Administration in progressive and severe renal disease
- Administration with sorbitol. Concomitant administration of both substances may lead to increased dehydratation (sorbitol might cause additional fluid loss by inducing diarrhoea)
- Administration in Lupus Erythematosus

- Medication that prolong the QT interval

Premature infants (possible development of nephrocalcinosis /nephrolithiasis; renal function must be monitored and renal ultrasonography performed). In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life can increase the risk of persistent ductus arteriosus Botalli.

Caution should be observed in patients liable to electrolyte deficiency.
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. (e.g. due to vomiting or diarrhoea).
Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

In patients who are at high risk for radiocontrast nephropathy, furosemide is not recommended to be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

**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).

Photosensitivity: Cases of photosensitivity reactions have been reported. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

This medicinal product contains 0.6mmol sodium per dose of 40mg. To be taken into consideration by patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

Not recommended combinations

Lithium:
Lithium excretion levels may be reduced by furosemide, resulting in increased cardiotoxic effect and lithium toxicity. Therefore, this combination is not recommended (see section 4.4). If this combination is deemed necessary lithium levels should be carefully monitored and lithium dosage should be adjusted.

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.

Combinations requiring a caution for use
Ototoxic drugs (e.g. aminoglycosides, cisplatin):
Furosemide may intensify the ototoxicity of certain drugs, for example cisplatin or aminoglycoside antibiotics such as kanamycin, gentamicin and tobramycin, in particular in patients with renal impairment. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

Chloral Hydrate:
In isolated cases, the intravenous administration of furosemide in a 24 hour period prior to chloral hydrate administration may lead to flush, hyperhidrosis, anxiety, nausea, increase in blood pressure and tachycardia. Therefore, the simultaneous administration of furosemide and chloral hydrate is not recommended.

Carbamazepine and aminoglutethimide:
Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Other anti-hypertensive agents:
The effect of other certain anti-hypertensive agents (diuretics and other drugs that low blood pressure) may be potentiated by concurrent administration of furosemide.

Inhibitors of the angiotensin converting enzyme (ACE) and Angiotensin II receptor antagonists:
The effects of other antihypertensives can be potentiated by concomitant administration of furosemide. Severe fall in blood pressure with shock in extreme cases and deterioration of renal function (acute renal failure in isolated cases) have been observed in combination with ACE inhibitors, when the ACE inhibitor was administered for the first time, or for the first time at high dosage (first dose hypotension). If possible, furosemide therapy should be temporarily discontinued (or at least the dose reduced) for three days before therapy with an ACE inhibitor or an Angiotensin II receptor antagonists is initiated or the dose of an ACE inhibitor or Angiotensin II receptor antagonists is increased.

Patients taking diuretics may suffer accentuated hypotension and deterioration of renal function; renal impairment may also occur during the first concurrent administration, or with the first administration of high doses of ACE or of an antagonist of the angiotensin II receptor.

Thiazides:
A synergetic effect of diuresis occurs as result of interaction of furosemide and thiazides.

Anti-diabetic agents:
A decrease in glucose tolerance may occur, since furosemide may reduce these drugs action.

Metformin:
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.

Cardiac glycosides (e.g. digoxin) and other medicinal products that may cause prolongation of the QT-interval:

A decrease of potassium levels may increase digitalis toxicity; for this reason, potassium levels should be monitored.
Some electrolyte disturbances may increase the toxicity of certain concomitantly administered drugs that may cause prolongation of the QT interval. e.g. (class Ia antiarrhythmics and class III antiarrhythmics like amiodarone, sotalol, dofetilide, ibutilide and quinolones). Monitoring of potassium plasma levels and ECG are recommended.

Fibrates:
Blood levels of furosemide and of fibric acid derivates (for example clofibrate and fenofibrate) may be increased during concurrent administration (particularly in case of hypoalbuminaemia). The increase of its effect/toxicity should be monitored.

Non-steroidal anti-inflammatory agents and high doses of salicylates:
Non-steroidal anti-inflammatory agents (including coxibs) may induce acute renal failure in cases of pre-existing hypovolaemia and reduce its diuretic, natriuretic and antihypertensive effect. When co-administered with high doses of salicylates,
the predisposition for salicylic toxicity may be increased due to a reduced renal excretion or to a modified renal function.

Nephrotoxic drugs (e.g. polymyxins, aminoglycosides, cephalosporins organoplatins, immunosuppressants, iodinated contrast media, foscarnet, pentamidine):

Furosemide may intensify the nephrotoxic effects of nephrotoxic drugs.
Antibiotics like cephalosporins-impairment of renal function may develop in patients receiving treatment with furosemide and high doses of certain cephalosporins.
There is a risk of cytotoxic effects if cisplatin and furosemide are given concomitantly.

In addition, Nephrotoxicity of cisplatin may be enhanced if furosemide in 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.

Drugs that undergo significant renal tubular secretion:
Probenecid, 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 these products. In case of high-dose treatment (in particular, of both furosemide and the other medicinal products), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

Peripheral adrenergic inhibitors:
These agents´ effects may be enhanced by the simultaneous administration of furosemide.

Phenobarbital and phenytoin:
Attenuation of the effect of furosemide may occur following concurrent administration of these drugs.

Tubocurarine, curarine derivatives and succinyl choline:
The muscle relaxing effect of these agents may be enhanced or prolonged by furosemide.

Glucocorticoids, carbenoxolone, Amphotericin B, Penicillin G, ACTH, laxatives and liquorice:
Co-administration of furosemide with glucocorticoids, carbenoxolone,large amount of liquorice or prolonge use of laxatives may increase potassium loss. In the association with glucocorticoids, hypokalaemia should be considered and its aggravation with the overuse of laxatives. Since, this may lead to irreversible hearing damages, this combination should only be used if there are compelling medical reasons.
Potassium levels should be monitored.

Sucralfate:
Simultaneous administration of sucralfate and furosemide may reduce the natriuretic and antihypertensive effects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate should be separated by at least two hours.

Oral anticoagulants:
Furosemid increases the effects of oral anticoagulants.

Theophylline:
The effects of theophylline and of curare-type muscle relaxants may be potentiated.

Pressor amines (e.g. adrenaline (epinephrine), noradrenaline (norepinephrine)):
Concomitant use of furosemide may attenuate the effects of pressor amines.

Other interactions:
Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

## 4.6 Fertility, pregnancy and lactation

Use during pregnancy
Furosemide should not be given during pregnancy unless there are compelling medical reasons. Furosemide crosses the placental barrier, and can therefore cause a diuresis of the fetus. Treatment during pregnancy requires monitoring of fetal growth.

Treatment of pregnancy hypertension and oedema is in general not recommended, as physiological hypovolemia can be induced which causes reduction of placental perfusion.
If use of furosemide is essential for the treatment of cardiac or renal insufficiency during pregnancy, careful monitoring of electrolytes, haematocrit and fetal growth is essential. Possible displacement of bilirubin from albumin binding and thus elevated risk of nuclear icterus in hyperbilirubinaemia is discussed for furosemide. Furosemide can predispose the fetus to hypercalciuria, nephrocalcinosis, and secondary hyperparathyroidism.

Furosemide reaches 100% of the maternal serum concentration in cord blood. No malformations in humans which might be associated with exposure to furosemide have been reported to date. However, there is limited experience to allow a conclusive evaluation of a potential damaging effect in the embryo/fetus.

Use during lactation
Furosemide passes into breast milk and may inhibit lactation. Women must not breast-feed if they are treated with furosemide (see section 4.3).

## 4.7 Effects on ability to drive and use machines

Furosemide has negligible influence on the ability to drive and use machines.
Patients respond individually to Furosemide.
The ability to drive or operate machines can incidentally be reduced because of treatment with furosemide, especially at the start of therapy, change of medication or in combination with alcohol.

## 4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:
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); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: thrombocytopenia; thrombocytopenia may become manifest, especially with an increase of haemorrhage tendency.
Rare: eosinophilia, leukopenia, bone marrow depression; occurrence of this symptom necessitates withdrawal of treatment.
Very rare: haemolytic anaemia, aplastic anaemia, agranulocytosis.
Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop especially in elder patients.

Immune system disorders
Rare: severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (for treatment see section 4.9).

Endocrine disorders
Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of the metabolic control; latent diabetes mellitus may become manifest.

Metabolism and nutrition disorders
Hypokalaemia, hyponatraemia and metabolic alkalosismay occur, especially after prolonged therapy or when high doses are administered. Regular monitoring of serum electrolytes (especially potassium, sodium and calcium) is therefore indicated.
Potassium depletion may occur, especially due to poor potassium diet. Particulary when the supply of potassium is concomitantly reduced and/or extrarenal potassium losses are increased (e.g. in vomiting or chronic diarrhoea) hypokalaemia may occur as a result of increased renal potassium losses.
Underlying disorders (e.g. cirrhotic disease or heart failure), concomitant medication (see section 4.5) and nutrition may cause predisposition to potassium deficiency. In such cases, adequate monitoring is necessary as well as therapy

substitution.

As a result of increased renal sodium losses, hyponatraemia with corresponding symptoms may occur, particularly if the supply of sodium chloride is restricted.

Increased renal calcium losses can lead to hypocalcaemia, which may induce tetania in rare cases.

In patients with increased renal magnesium losses, tetania or cardiac arrhythmias were observed in rare cases as a consequence of hypomagnesaemia.

Uric acid levels may increase and gout attacks may occur.

Metabolic alkalosis may develop, or pre-existing metabolic alkalosis (for e.g. decompensated hepatic cirrhosis) may become more severe with furosemide.

Nervous system disorders
Rare: paraesthesia, vertigo, dizziness, sleepiness, confusion, sensations of pressure in the head.

Eye disorders
Rare: aggravation of myopia, blurred vision; disturbances of vision with hypovolaemia symptoms.

Ear and labyrinth disorders
Rare: dysacusis and/or syrigmus (tinnitus aurium) due to furosemide are rare and usually transitory; incidence is higher in rapid intravenous administration, particularly in patients with renal failure or hypoproteinaemia (e.g. in nephrotic syndrome).

Cardiac disorders
In particular, at the initial state of treatment and in elderly, a very intense diuresis may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as orthostatic hypotension, acute hypotension, sensations of pressure in the head, dizziness, circulatory collapse, thrombophlebitis or sudden death (with i.m. or i.v. administration).

Gastrointestinal disorders
Rare: nausea, vomiting, diarrhoea, anorexia, gastric distress, constipation, dry mouth.

Hepato-biliary disorders
Very rare: acute pancreatitis, intrahepatic cholestasis, cholestasis jaundice, hepatic ischaemia, increases in hepatic transaminases.

Skin and subcutaneous tissue disorders
Uncommon: pruritus, dermal and mucosal reactions (e.g. bullous exanthema, rash, urticaria, purpura, erythema multiforme, exfoliative dermatitis, photosensitivity)
Rare: vasculitis, lupus erythematosus exacerbation or activation.

Musculoskeletal and connective tissue disorders
Rare: leg muscle cramps, asthenia. chronic arthritis.

Renal and urinary disorders
Diuretics may exacerbate or reveal acute retention of urine symptoms (bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), vasculitis, glycosuria, transitorily increase of blood creatinine and urea levels.
Rare: interstitial nephritis.

Pregnancy, puerperium and perinatal conditions
Premature infants treated with furosemide may develop nephrocalcinosis and/or nephrolithiasis; due to calcium deposit in renal tissue.
In premature infants with respiratory distress syndrome, diuretic treatment in the first weeks of life with furosemide can

increase the risk of persistent ductus arteriosus Botalli.

General disorders and administration site conditions
Rare: febrile conditions; following i.m. injection local reactions such as pain may appear.

Investigations
Rare: serum cholesterol and triglyceride levels may rise during furosemide treatment.

## 4.9 Overdose

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 - including AV blockage and ventricular fibrillation) due to excessive diuresis.

**Symptoms:**
Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

**Treatment:**
At the first signs of shock (hypotension, sudoresis, nausea, cyanosis) the injection should be immediately interrupted, place the patient head down and allow free breathing.
Fluid replacement and correction of the electrolyte imbalance; monitoring of metabolic functions, and maintenance of urinary flux.

Medicinal treatment in case of anaphylactic shock: dilute 1 ml of 1:1000 adrenaline solution in 10 ml and inject slowly 1 ml of the solution (corresponding to 0.1 mg of adrenaline), control pulse and tension and monitor eventual arrhythmias. Adrenaline administration may be repeated, if necessary. Subsequently, inject intravenously a glucocorticoid (for example 250 mg of methylprednisolone), repeating if necessary.

Adapt the above-mentioned dosages for children, according body weight.

Correct hypovolaemia with available means and complement with artificial ventilation, oxygen and in case of anaphylactic shock with anti-histamines.

No specific antidote to furosemide is known. If overdose during parenteral treatment has taken place, in principle the treatment consists on follow up and supportive therapy. Haemodialysis does not accelerate furosemide elimination.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretic, Sulfonamides, plain
ATC code: CO3C A01
Furosemide is a strong diuretic agent of fast action. From a pharmacological point of view, furosemide inhibits the co-transport system (reabsorption) of the following electrolytes $Na^+$, $K^+$ and $2CL^-$, located on the luminal cell membrane on the ascending limb of the loop of Henle. Consequently, furosemide´s efficiency depends on the drug reaching the tubular lumen through an anionic transport mechanism. The diuretic effect results on the inhibition of sodium chloride reabsorption in this segment of the loop of Henle. As a result, the fraction of excreted sodium may ascend to 35% of sodium glomerular filtration. The secondary effects of increased elimination of sodium are: increase of urinary excretion and increase of potassium distal secretion at the distal tube. Excretion of calcium and magnesium salts is also increased.

Furosemide inhibits the feedback mechanism in the dense macula and induces dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In case of heart failure, furosemide induces an acute reduction of cardiac pre-load (through the enlargement of the

blood vessels capacity). This early vascular effect seems to be mediated by prostaglandins and assumes an adequate renal function with activation of the renin-angiotensin system and an intact synthesis of prostaglandins. Due to its natriuretic effect, furosemide reduces the vascular reactivity to catecholamine that is increased in hypertensive patients.

The diuretic effect of furosemide is established within 15 minutes of an intravenous administration.

A dose-dependent increase in diuresis and natriuresis was found in healthy individuals to whom furosemide was administerd (doses between 10 and 100 mg). The duration of action in healthy individuals after the administration of an intravenous 20 mg dose of furosemide is approximately 3 hours and 3 to 6 hours, when an oral 40 mg dose is given.

In ill patients, the relation between tubular concentration of free furosemide and bound furosemide (determined through the urine excretion rate) andits natriuretic effect is translated in a sigmoid graphic, with a minimum effective excretion rate of approximately 10 micrograms per minute. Consequently, a continuous infusion of furosemide is more effective than repeated bolus injections. Above a certain bolus administration dose, the drugs effects do not significantly increase. The efficacy of furosemide is decreased in cases of reduced tubular secretion or in cases of intra-tubular binding of the drug to albumin.

## 5.2 Pharmacokinetic properties

Distribution
Furosemide distribution volume is 0.1 to 1.2 litres per kg of body weight. The distribution volume may be increased depending on the concomitant illness.
Protein binding (mostly to albumin) is higher than 98%.

Elimination
Furosemide is mostly eliminated as the non-conjugated form, mainly through secretion at the proximal tube. After intravenous administration, 60% to 70% of furosemide is eliminated by this manner. The glucuronic metabolite of furosemide represents 10% to 20% of the recovered substances in the urine. The remaining dose is eliminated in the faeces, probably after biliary secretion. After intravenous administration, the plasma half-life of furosemide ranges from 1 to 1.5 hours.
Furosemide is excreted in breast milk. It crosses the placental barrier transferring itself slowly to the foetus. Furosemide achieves similar concentrations in the mother, foetus and newborn.

Renal impairment
In case of renal impairment, furosemide´s elimination is slower and its half-life is increased. In patients with end-stage renal disease the average half-life is 9.7 hours. In several multi-organ failure the half life may range from 20-24 hours.
In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unbound furosemide . On the other hand, the efficiency of furosemide is reduced in these patients, due to intratubular albumin binding and to reduced tubular secretion.
Furosemide exhibits low dialysis in patients undergoing haemodialysis, peritoneal dialysis or CAPD (Chronic Ambulatory Peritoneal Dialysis).

Hepatic impairment
In case of hepatic impairment, furosemide´s half-life increases 30% to 90%, mainly due to the higher distribution volume. Biliary elimination might be reduced (up to 50%). In this group of patients, there is a wider variability of the pharmacokinetic parameters.

Congestive heart failure, severe hypertension, elderly
Furosemide elimination is slower due to reduced renal function in patients with congestive heart failure, severe hypertension or in elderly.

Premature infants and new-born
Depending on the maturity of the kidney, elimination of furosemide may be slow. In case of children with insufficient capacity of glucuronidation, the metabolism of the drug is also reduced. In term neonates the half-life is generally less than 12 hours.

## 5.3 Preclinical safety data

Chronic toxicity studies in the rat and dog led to renal alterations (among others fibrous degeneration and renal calcification). Furosemide did not show genotoxic or carcinogenic potential.
In reproductive toxicology studies, a reduced number of differentiated glomeruli, skeletal anomalies of the scapulae, humerus and ribs (induced by hypokalaemia) were seen in fetal rats, as well as hydronephrosis that occurred in fetal mice and rabbits after administration of high doses. The results of a mouse study and one of the three rabbit studies showed an increased incidence and severity of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from the treated dams as compared with those from the control group.
Preterm rabbits given furosemide had a higher incidence of intraventricular haemorrhage than saline-treated littermates, possibly due to furosemide-induced intracranial hypotension.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium hydroxide
Sodium chloride
Hydrochloric acid
Water for Injections

## 6.2 Incompatibilities

Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions). This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

Shelf life of the finished medicinal product: 4 years
After first opening: Once opened the product should be used immediately.

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC protected from light. 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Keep in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

## 6.5 Nature and contents of container

2 ml or 5 ml, Type I amber glass ampoules.

Pack sizes:
5, 100 x 2 ml ampoules
5, 50 x 5 ml ampoules
Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Furosemide Injection diluted to 0.6 mg/ml is compatible with 0.90% NaCl Infusion, and Compound Sodium Lactate Infusion for 24 hrs. The dilution of the solution for injection is to be made under aseptic conditions.

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles. Any unused product or waste material should be disposed of in accordance with local requirements. For single use only, discard any remaining contents after use.

Furosemide 10 mg / ml Solution for Injection solution should not be mixed with any other drugs in the injection bottle.

## 7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

## 8 MARKETING AUTHORISATION NUMBER

PA 822/26/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 21st December 2011

## 10 DATE OF REVISION OF THE TEXT