1. NAME OF THE MEDICINAL PRODUCT

Furosemide 20 mg/2 ml solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains 20 mg of furosemide corresponding to 10 mg furosemide per ml.

Excipient with known effect:
This medicinal product contains 3.7 mg sodium per ml.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless to almost colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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)

The parenteral administration of furosemide is indicated for use in cases where a prompt and effective diuresis is required or oral administration is not feasible or not efficient.

4.2 Posology and method of administration

Posology:
The lowest dose with which the desired effect is achieved should always be used.
The duration of the treatment should be determined by the doctor and be appropriate to the type and severity of the disease.

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.

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.

Intravenous administration of furosemide must be slow; 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.

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

If there is no opposing medical advice, the initial dose recommended for adults and *adolescents* over 15 years, is of 20 to 40 mg (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 is 1500 mg**.**

Weight loss induced by enhanced diuresis should not exceed 1 kg/day.

Paediatric population

Children and adolescents (up to 18 years of age):
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.

Patients with 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 per minute is not exceeded.

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

Special dosage recommendations

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 40mg 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 1500 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.

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.

Oedema associated to 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. This dose may produce in adults a daily body weight loss of approximately 0.5 kg.

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.

Method of administration
For instructions 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.

- Hypersensitivity to sulphonamider (e.g. Sulfonylureas or antibiotics of sulphonamides group)
- Renal failure with oligoanuria not responding to furosemide.
- Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents.
- Pre-comatose and comatose state associated with hepatic encephalopathy.
- Severe hypokalaemia (see section 4.8).
- Severe hyponatraemia.
- Hypovolaemia with or without hypotension.
- Dehydration.
- Breast-feeding (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. patients with prostatic hypertrophy). 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 it's ototoxicity increased)
- Co-administration with lithium salts (monitoring of lithaemia 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)
- Premature infants (possible development 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.
- NSAIDs may antagonise the diuretic effect of furosemide and other diuretics. Use of NSAIDs with diuretics may increase the risk of nephrotoxicity

Cautious dose titration is required.

- Electrolyte variations (e.g. hypokalaemia, hyponatraemia)
- Fluid variations, dehydration, blood volume reduction with circulatory
- collapse and possibility of thrombosis and embolism, particularly in elderly, with excessive use;
- Ototoxicity (if administered faster than 4 mg/ml) – 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 dehydration (sorbitol might cause additional fluid loss by inducing diarrhea)
- Administration in patients with systemic Lupus Erythematosus because of the possibility of exacerbation or activation of SLE
- Medication that prolong the QT interval

Particular caution and/or dose reduction is 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.

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 cases of significant additional fluid loss (e.g. due to vomiting or diarrhea).
Hypovolaemia or dehydration as well as any significant electrolyte or acid-base disturbances must be corrected.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of thiazide is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Athletes
The attention of athletes should be drawn to the fact that this drug contains an active ingredient which may interfere with doping tests by forced diuresis of the doping agents.

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).

Sodium content
This medicinal product contains 3.7 mg sodium per ml, equivalent to 0.2% 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

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. 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.

Levothyroxine:
High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

Combinations requiring a caution for use
Drugs with an increased risk of QTc-prolongation and torsades-de-pointes linked to hypokalaemia
Furosemide-induced electrolyte disturbances (hypokalaemia, hypomagnesaemia and hypocalcaemia) can cause QT prolongation and therefore the risk of arrhythmias is increased when concomitantly given with active substances that prolong the QT interval or produce hypokalaemia like:

- **class I and class III antiarrhythmics** (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, ibutilide, dofetilide),
- **cardiac glycosides** (digoxin), concurrent administration of furosemide increases cardiac toxicity of cardiac glycosides and may lead to fatal arrhythmias,
- **antipsychotics** (like sultopride, phenothiazines [e.g. chlorpromazine, thioridazine, trifluoperazine], benzamides [amisulpride, sulpiride], butyrophenones [e.g. droperidol, haloperidol],
- other **neuroleptics** [pimozide],
- other **miscellaneous substances** [e.g. bepridil, cisapride, erythromycin, halofantrine, sparfloxacine, pentamidine, quinolone etc.].

For this reason monitoring of potassium plasma levels and ECG should be made when these medicinal substances are prescribed concomitantly.

Medicinal substances decreasing serum potassium
Co-administration of furosemide with **amphotericin B, glucocorticoids, carbenoxolone, tetracosactide,** or **laxatives** may increase potassium loss. **Liquorice** has the same effect as carbenoxolone. 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.

Medicinal substances decreasing serum sodium
Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

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 the diuretic, natriuretic and antihypertensive effect of furosemide. 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.

Inhibitors of the angiotensin converting enzyme (ACE) and Angiotensin II antagonists (ARA)
The hypotensive effects and/or renal effects are potentiated when concomitantly given with furosemide. Reduction or interruption of furosemide therapy is recommended at least three days before initiating administration of ACE inhibitors and ARAs. Renal impairment may also occur during the first concurrent administration, or with the first administration of high doses of an ACE inhibitor or of an antagonist of the angiotensin II receptor.

Drugs that increase the antihypertensive effect of furosemide
The effect of ***other*** certain anti-hypertensive agents (other diuretics and other drugs that low blood pressure like beta-blocker) may be potentiated by concurrent administration of furosemide.

The potential for an additive effect between furosemide and amifostine, baclofen or alpha-blocker regarding hypotensive effects exists.

There is an increased risk of postural hypotension when loop diuretics like furosemide and tricyclic antidepressants (e.g. imipramine, nortriptyline, amitriptyline) or antipsychotic agents are given concomitantly.

Anti-diabetic agents
A decrease in glucose tolerance may occur, since furosemide may attenuate the effect of the anti-diabetic agents. Adjustment of the dose of antihyperglycaemic medications may be needed.

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.

Fibrates
Blood levels of furosemide and of fibric acid derivates (such as clofibrate and fenofibrate) may be increased during concurrent administration (particularly in case of hypoalbuminaemia, e.g. in nephrotic syndrome). The increase of its effects (increased diuresis and muscle symptoms) should be monitored.

Iodinated contrast media
In patients with risk factors like raised S-creatinine levels, dehydration, congestive heart failure, age over 70 years old or concurrent administration of nephrotoxic drugs the concomitant administration of furosemide and iodinated contrast media may increase the risk of contrast media associated acute renal failure and should therefore be avoided.

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.

Colestyramine and colestipol
These drugs may reduce furosemides bioavailability.

Nephrotoxic / ototoxic agents
Furosemide may intensify the nephrotoxic effects of nephrotoxic drugs (e.g. cephaloridine, cephalothin, ceftazidime, polymyxins, aminoglycosides, organo-platins, immunosuppressants, foscarnet, pentamidine).

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 ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, 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.

Furosemide may also intensify the ototoxicity of certain drugs, for example aminoglycosides and 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.

Neuromuscular blocker
Small doses of furosemide (less than 100 µg/kg) may potentiate neuromuscular blockade of competitive neuromuscular blocker (curare-type muscle relaxants like atracurium and tubocurarine) and depolarising neuromuscular blocker (like succinylcholine), whereas high doses may result in antagonism of neuromuscular blockade. The potassium-depleting effect of diuretics may enhance the effect of competitive neuromuscular blocker.

Other diuretics (potassium-sparing such as amiloride, triamterene)
Concurrent administration of furosemide and potassium-sparing diuretics may lead to a synergistic effect regarding diuresis. Sodium excretion may increase and potassium excretion may decrease.

Theophylline
Theophylline's clearance has been found to be deceased by around 20% by concurrent administration of furosemide thereby potentiating the effects of theophilline. There is an increased risk of hypokalaemia when given concomitantly with furosemide.

Thiazides
A synergetic effect of diuresis, sodium and potassium excretion occurs as result of interaction of furosemide and thiazides resulting in an increased risk of dehydration, hyponatraemia and hypokalaemia.

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. Controversially, furosemide may decrease renal elimination of these substances. In case of high-dose treatment (in particular of both furosemide and the other substances), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

Anticonvulsants
Attenuation of the effect of furosemide may occur following concurrent administration of anticonvulsants (e.g. phenytoin, phenobarbital).

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

Other interactions
Concomitant use of ciclosporin and diuretics is associated with an increased risk of gouty arthritis secondary to furosemide induced hyperuricemia and insufficient renal excretion of urates associated to ciclosporin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since furosemide crosses the placenta, it should be used during pregnancy for short periods and in compelling indications only.

Diuretics are not suitable for routine therapy of hypertension and oedema during pregnancy, as they impair placental perfusion and, consequently, foetal growth.

Treatment during pregnancy requires monitoring of electrolytes, haematocrit and foetal growth.

In animal studies, reproductive toxicity was observed (see section 5.3).

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 concluding evaluation of a potential damaging effect in the embryo/foetus.

If used during pregnancy, furosemide can predispose the foetus to hypercalciuria, nephrocalcinosis, and secondary hyperparathyreosis. In utero urinary production can also be stimulated in the foetus.

Breastfeeding
Furosemide is excreted into breast milk and inhibits lactation. In such cases, breast-feeding is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients respond individually to furosemide, and by causing fall in blood pressure it may reduce ability to drive or operate dangerous machinery. This risk is higher at the initial state of treatment, in medicinal changes and with alcohol.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction for Furosemide is hepatic encephalopathy in patients with hepatocellular insufficiency (see section 4.3).
In uncommon cases deafness which is sometimes irreversible has been reported.

Tabulated list of adverse reactions

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).

As with other diuretics, certain undesirable effects may occur, such as:

System Organ Class	**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)**	**Frequency not known (cannot be estimated from available data)**
Blood and lymphatic system disorders		Thrombocytopenia[1]	bone marrow depression[2], eosinophilia, leukopenia	haemolytic anaemia, aplastic anaemia, agranulocytosis	
Immune system disorders			severe anaphylactic and anaphylactoid reactions such as anaphylactic shock[3]		exacerbation or activation of systemic lupus erythematosus
Nervous system disorders	hepatic encephalopathy in patients with hepatocellular insufficiency[4]		paraesthesia, vertigo, sleepiness, confusion, sensations of pressure in the head		Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension or by other causes), headache
Eye disorders			blurred vision, disturbances of vision with hypovolaemia symptoms		
Ear and labyrinth disorders		deafness (sometimes irreversible)	dysacusis and/or tinnitus aurium[5]		

Gastrointestinal disorders			nausea, vomiting and diarrhoea, anorexia, gastric distress, constipation, dry mouth	acute pancreatitis	
Skin and subcutaneous tissue disorders		pruritus, dermal and mucosal reactions[6]	vasculitis		Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), DRESS (Drug rash with eosinophilia and systemic symptoms)
Musculoskeletal and connective tissue disorders			leg muscle cramps, asthenia, decrease of calcium serum levels, chronic arthritis	tetany	cases of rhabdomyolysis have been reported, frequently related to severe hypokalemia (see section 4.3)
Renal and urinary disorders			interstitial nephritis		
General disorders and administration site conditions			febrile conditions, local pain following i.m. injection		
Investigations			increased serum cholesterol and triglyceride		

[1] May become manifest, especially with an increase of haemorrhage tendency.
[2] If this occurs, treatment should be discontinued.
[3] For treatment see section 4.9.
[4] See section 4.3.
[5] Tinnitus may occur transitory.
[6] For example bullous exanthema, rash, urticaria, purpura, erythema multiforme, exfoliative dermatitis, photosensitivity.

Description of the selected adverse reactions

Blood and lymphatic system disorders
The diuretic action of furosemide may lead to or contribute to hypovolaemia and in severe cases to dehydration especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

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

Metabolism and nutrition disorders
Electrolyte and water balance may be disturbed (hypokalaemia, hyponatraemia and metabolic alkalosis), 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. Particularly 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. This is manifested as neuromuscular (myasthenia, paraesthesia, pareses), intestinal (vomiting, constipation, meteorism), renal (polyuria, polydipsia) and cardiac (impaired paced setting and conduction disorders) symptoms. Severe potassium losses may lead to paralytic ileus or disturbed consciousness, with coma in extreme cases. Furthermore, 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. Commonly observed symptoms of sodium deficiency are apathy, systremma, inappetence, asthenia, somnolence, vomiting and confusion.

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

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

Certain patients may present increased uric acid levels and gout attacks may occur.

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

Ear and labyrinth disorders
Incidence of tinnitus aurium 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).

Hepato-biliary disorders
Intrahepatic cholestasis, cholestatic jaundice, hepatic ischaemia, increase in hepatic transaminases.

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.

Pregnancy, puerperium and perinatal conditions
Premature infants treated with furosemide may develop nephrolithiasis and/or nephrocalcinosis, 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.

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

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 a delirious status, severe hypotension (progressing to shock), acute renal failure, thrombosis, flaccid paralysis, apathy and confusion.

b) 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 adrenalin solution in 10 ml and inject slowly 1 ml of the solution (corresponding to 0,1 mg of adrenalin), control pulse and tension and monitor eventual arrhythmia. Adrenalin

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 to 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: High-ceiling diuretic
ATC Code: C03C A01

Mechanism of action
Furosemide is a strong diuretic agent~~,~~ of fast action. From a pharmacological point of view, Furosemide inhibits the co-transport system (re-absorption) of the following electrolytes Na^+, K^+ and $2Cl^-$, located on the luminal's 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 re-absorption in this segment of the loop of Henle. As a result, the fraction of excreted sodium may ascend to 35% of sodium's 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 are 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 enlarged in hypertensive patients.

The antihypertensive effect of furosemide is attributed to the increase in sodium excretion, to the reduction of blood volume and to the vascular smooth muscle response to vasoconstriction stimulation.

Pharmacodynamic effects

The diuretic effect of furosemide is established within 15 minutes of an intravenous administration and within 1 hour of an oral administration.

A dose-dependent increase in diuresis and natriuresis was found in healthy individuals to whom furosemide was administered (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) and it's 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-tube binding of the drug to albumin.

5.2 Pharmacokinetic properties

Distribution

Furosemide distribution volume is 0,1 to 1,2 liters 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%.

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 or newborn.

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.

Renal Impairment

In case of renal impairment, furosemide's elimination is slower and its half-life is increased. The terminal half-life may achieve 24 hours in patients with renal impairment.

In case of nephrotic syndrome, the lower concentration of plasmatic proteins leads to higher concentrations of non-conjugated furosemide (free). On the other hand, the

efficiency of furosemide is reduced in these patients, due to intratubular albumin binding and to reduced tubular secretion.

Furosemide suffers 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

Furosemides 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 by 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. In children with 2 or more months of age, terminal clearance is identical to adults.

5.3 Preclinical safety data

Acute oral toxicity was low in all species tested. Chronic toxicity studies in the rat and dog led to renal alterations (among others fibrous degeneration and renal calcification).

In vitro and in vivo tests of genetic toxicology did not reveal any clinically relevant evidence of a genotoxic potential of furosemide.

Long-term studies in mice and rats did not yield any relevant evidence of a tumourigenic potential.

In studies of reproductive toxicology in foetal rats, a reduced number of differentiated glomeruli, skeletal anomalies of the scapulae, humerus and ribs (induced by hypokalaemia), as well as hydronephrosis occurred in foetal 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 foetuses derived from the treated dams as compared with the incidence in foetuses 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 chloride

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Furosemide should not be mixed with strong acid solutions (pH lower than 5.5), such as solutions containing ascorbic acid, noradrenaline and adrenaline, due to the risk of precipitation.

This medicinal product must 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:

3 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 25 ºC 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 the ampoules in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

2 ml, Type I amber glass ampoules.

Each pack contains:

5 ampoules

50 ampoules

100 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Furosemide injection may be mixed with neutral and weak alkaline solution with pH between 7 and 10, such as 0.9% sodium chloride and Ringer's lactate solution.

Product containing visible particles should not be used.

For single use only, discard any remaining contents after use.

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

7 MARKETING AUTHORISATION HOLDER

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