1. NAME OF THE MEDICINAL PRODUCTS

Lasix® 20 mg solution for injection
Lasix® 40 mg solution for injection
Lasix® 250 mg solution for infusion

Active substance: furosemide sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lasix 20 mg solution for injection
Each ampoule with 2 ml solution for injection contains 21.3 mg furosemide sodium (equivalent to 20 mg furosemide).
Excipient with known effect:
Contains sodium (see section 4.4).

Lasix 40 mg solution for injection
Each ampoule with 4 ml solution for injection contains 42.6 mg furosemide sodium (equivalent to 40 mg furosemide).
Excipient with known effect:
Contains sodium (see section 4.4).

Lasix 250 mg solution for infusion
Each ampoule with 25 ml solution for infusion contains 266.6 mg furosemide sodium (equivalent to 250 mg furosemide).
Excipient with known effect:
Contains sodium (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection / solution for infusion
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lasix 20 mg/40 mg solution for injection
Lasix 20 mg or 40 mg solution for injection is indicated when adequate diuresis is not achieved with oral administration of furosemide or when oral use is not possible:

- oedemas and/or ascites resulting from disorders of the heart or liver
- oedemas due to disorders of the kidneys
- oedemas due to burns
- pulmonary oedema (e.g. in acute heart failure)
- supporting measure in cerebral oedema
- oliguria as a result of a gestosis, if necessary after correction of a volume deficiency state (oedemas and/or hypertension in gestoses are not an indication!)
- hypertensive crisis (in addition to other therapeutic measures)

Lasix 250 mg solution for infusion
The use of the high-dose preparation Lasix 250 mg solution for infusion is indicated exclusively for patients with greatly reduced glomerular filtration (glomerular filtration values less than 20 ml/min).

- Imminent and already existing acute renal failure (to maintain fluid excretion and to facilitate parenteral feeding, provided there is still residual filtration)
- Chronic renal failure in the predialytic stage with fluid retention and hypertension
- Terminal renal failure: to maintain residual diuresis
- Nephrotic syndrome in patients who do not respond to an oral dose of 120 mg furosemide/day (treatment of the underlying disorder is the primary consideration here).

4.2 Posology and method of administration

The dosage should be tailored to individual needs, especially according to the success of therapy. The lowest dose at which the desired effect is obtained should always be used.

For adults the following dosage guidelines apply:

Lasix 20 mg/40 mg solution for injection

Dosage

Oedemas and/or ascites resulting from disorders of the heart or liver:

Initial dose 2-4 ml
(equivalent to 20-40 mg furosemide) IV.
With oedemas that are difficult to mobilise, this dose can be repeated at appropriate intervals until the onset of diuresis.

Oedemas due to disorders of the kidneys:
Initial dose 2-4 ml
(equivalent to 20-40 mg furosemide) IV.
With oedemas that are difficult to mobilise, this dose can be repeated at appropriate intervals until the onset of diuresis.

In nephrotic syndrome the dose must be carefully determined because of the risk of increased side effects.

Oedemas due to burns:
The daily and/or single dose may be between 4 and 10 ml (equivalent to 40-100 mg furosemide), in exceptional cases of impaired renal function up to 25 ml (equivalent to 250 mg furosemide). Intravascular volume deficiency must be corrected before using Lasix 20 mg or 40 mg solution for injection.

Pulmonary oedema (e.g. in acute heart failure):
Use in conjunction with other therapeutic measures. Initial dose 2-4 ml (equivalent to 20-40 mg furosemide) IV.

If an increase in diuresis is still not achieved, administration can be repeated after 30-60 minutes, where necessary doubling the dose.

As a supporting measure in cerebral oedema:
The daily and/or single dose may be between 4 and 10 ml (equivalent to 40-100 mg furosemide). In exceptional cases of impaired renal function up to 25 ml (equivalent to 250 mg furosemide) may be administered.

Oliguria due to a gestosis:
The expected benefits must be very carefully weighed against possible risks. Intravascular volume deficiency must be corrected before using Lasix 20 mg or 40 mg solution for injection.

The dose may be between 1 and 10 ml (equivalent to 10-100 mg furosemide) daily.

Oedemas and/or hypertension in gestoses are not an indication for Lasix 20 mg or 40 mg solution for injection.

Hypertensive crisis:
2-4 ml (equivalent to 20-40 mg furosemide) in addition to other therapeutic measures.

Use in children:
Infants and children under 15 years old should be given Lasix by the parenteral route only as an exception in threatening situations. The average daily dose is 0.5 mg furosemide/kg body weight. By way of exception, up to 1 mg furosemide/kg body weight can be injected intravenously.

Method of administration and duration of use
Lasix 20 mg and 40 mg solution for injection are usually given intravenously. In exceptional cases in which neither oral nor intravenous administration is possible, Lasix 20 mg or 40 mg solution for injection can be administered by the intramuscular route, but not in acute situations (e.g. not in pulmonary oedema) and not in high doses.

With intravenous administration, Lasix 20 mg or 40 mg solution for injection should be injected slowly. The injection speed of 0.4 ml solution for injection (equivalent to 4 mg furosemide) per minute must not be exceeded. In patients with advanced renal failure (serum creatinine >5 mg/dl) the injection speed should not exceed 0.25 ml solution for injection per minute (equivalent to 2.5 mg furosemide per minute). In cases where it is necessary to increase the dose to 25 ml (equivalent to 250 mg furosemide), this dose should be administered by means of a perfusor. If necessary the solution for injection can be diluted with isotonic saline solution.

Lasix 20 mg or 40 mg solution for injection must not be mixed with other medicinal products in the same syringe.

Care must be taken to ensure that the pH of the ready-to-use injection solution is in the weakly alkaline to neutral range (pH not below 7). Acid solutions must not be used as the active substance may precipitate.

Lasix 250 mg solution for infusion

Dosage

Acute renal failure:

In patients with shock, hypovolaemia and hypotension must be eliminated before the start of treatment by taking appropriate measures. Similarly, a markedly pronounced disturbance of serum electrolytes and the acid-base equilibrium must be corrected. If a test dose of 40 mg furosemide, injected slowly by the intravenous route, does not bring about increased water excretion, treatment with Lasix 250 mg solution for infusion can be started.

50-100 mg furosemide per hour may be administered over the day using a perfusor. The daily dose should be tailored to provide adequate diuresis, but the maximum dose should not exceed 1500 mg furosemide per day.

Chronic renal failure in the predialytic stage with fluid retention and hypertension, nephrotic syndrome:
As the natriuretic response depends on numerous variables, e.g. the degree of renal failure, sodium balance etc. and cannot therefore in principle be predicted precisely in individual cases, the correct dose is best determined by increasing the dose gradually. Because of the rapid onset of action, the dose can be stepped up at ½ to hourly intervals. The recommended initial dose should be 0.1 mg per minute in the form of an infusion. As in patients with chronic renal failure the mobilisation of fluids should take place slowly, the dose should be selected so that the patient loses about 1 kg weight (140 mmol Na^+) per day on average.

In nephrotic syndrome the dose must be carefully determined because of the risk of increased side effects.

Use in children:
Infants and children under 15 years old should be given Lasix by the parenteral route only as an exception in threatening situations. The average daily dose is 0.5 mg furosemide/kg body weight. By way of exception, up to 1 mg furosemide/kg body weight may be administered intravenously.

Method of administration and duration of use
Lasix 250 mg solution for infusion should usually be administered by means of a perfusor. The infusion rate of 0.4 ml Lasix 250 mg solution for infusion per minute (equivalent to 4 mg furosemide per minute) must not be exceeded. In patients with advanced renal failure (serum creatinine >5 mg/dl) the infusion speed should not exceed 0.25 ml Lasix 250 mg solution for infusion per minute (equivalent to 2.5 mg furosemide per minute). If necessary, the solution for infusion can be diluted with isotonic saline solution.

The solution for infusion must not be infused together with other medicinal products.

Care must be taken to ensure that the pH of the ready-to-use solution for infusion is in the weakly alkaline to neutral range (pH not below 7). Acid solutions must not be used as the active substance may precipitate.

Lasix 20 mg/40 mg solution for injection / Lasix 250 mg solution for infusion
The ready-to-use preparation was found to be chemically and physically stable for 24 hours at 25 °C. From the microbiological standpoint, the ready-to-use preparation must be administered immediately.

If the ready-to-use preparation is not employed immediately, the user is responsible for the duration and conditions of storage.

In order to achieve optimum efficacy and suppress a counter-regulatory reaction, a continuous infusion of furosemide should be selected in preference to the repeated administration of injections.

Furosemide is only administered intravenously if oral application is not possible or is ineffective (e.g. in patients with poor intestinal absorption) or a rapid effect is required. Parenteral administration of Lasix should be replaced by oral use as soon as treatment permits.

The duration of use depends on the nature and severity of the disorder.

4.3 Contraindications

Lasix 20 mg/40 mg solution for injection
Lasix 20 mg and 40 mg solution for injection must not be used in:

- hypersensitivity to furosemide, sulfonamides (possible cross allergy with furosemide) or any of the excipients listed in section 6.1
- renal failure with anuria refractory to furosemide therapy
- hepatic coma and precomatose states associated with hepatic encephalopathy
- severe hypokalaemia
- severe hyponatraemia
- hypovolaemia or dehydration
- nursing mothers.

Lasix 250 mg solution for infusion
Lasix 250 mg solution for infusion must not be used in:

- normal renal function or impaired renal function with glomerular filtration values greater than 20 ml/min, because in these cases there is a risk of a too pronounced water and electrolyte loss
- hypersensitivity to furosemide, sulfonamides (possible cross allergy with furosemide) or any of the excipients listed in section 6.1
- renal failure with anuria refractory to furosemide therapy
- hepatic coma and precomatose states associated with hepatic encephalopathy
- severe hypokalaemia
- severe hyponatraemia
- hypovolaemia or dehydration
- nursing mothers.

Lasix 250 mg solution for infusion must not be used for bolus injection. It must be infused while monitoring the infusion volume and rate to reduce the risk of accidental overdosage.

4.4 Special warnings and precautions for use

Particularly careful monitoring is necessary in:

- patients with hypotension
- patients with manifest or latent diabetes mellitus (regular monitoring of the blood sugar level)
- patients with gout (regular monitoring of the uric acid in the serum)
- patients with impairment of micturition (e.g. in prostatic hypertrophy, hydronephrosis, ureter stenosis)
- patients with hypoproteinaemia, e.g. in nephrotic syndrome (careful adjustment of the dose)
- patients with hepatorenal syndrome (rapidly progressing renal insufficiency combined with severe hepatic disease, e.g. liver cirrhosis)
- patients who are particularly at risk from an unwanted severe fall in blood pressure, e.g. those with cerebrovascular circulatory disorders or coronary heart disease
- premature infants (risk of developing nephrocalcinosis/nephrolithiasis; monitoring of renal function, nephrosonography).

In premature infants with respiratory distress syndrome, diuretic treatment with furosemide in the first weeks of life can increase the risk of persistent ductus arteriosus.

In patients with micturition disorders (e.g. in patients with prostatic hyperplasia) furosemide may only be used if provision has been made for a free flow of urine, because a sudden flood of urine can lead to urinary retention with overextension of the bladder.

Furosemide leads to increased excretion of sodium and chloride and, consequently, of water. Excretion of other electrolytes (particularly potassium, calcium and magnesium) is also increased. As disturbances in the fluid and electrolyte imbalance are frequently observed during therapy with Lasix as a result of increased electrolyte excretion, regular monitoring of serum electrolytes is indicated.

Particularly during long-term therapy with Lasix the serum electrolytes (especially potassium, sodium, calcium), bicarbonate, creatinine, urea and uric acid as well as the blood sugar should be regularly monitored.

Particularly close supervision is necessary for patients with a high risk of developing electrolyte disorders or in the case of severe fluid depletion (e.g. as a result of vomiting, diarrhoea or intensive sweating). Hypovolaemia or dehydration as well as pronounced electrolyte disturbances or impairment of the acid-base balance must be corrected. This may necessitate the temporary discontinuation of treatment with furosemide.

The possible development of electrolyte disturbances is influenced by underlying diseases (e.g. liver cirrhosis, heart

failure), co-medication (see section 4.5) and diet.

The weight loss caused by increased urine excretion should not exceed 1 kg/day irrespective of the extent of urine excretion.

In nephrotic syndrome the dose must be carefully determined because of the risk of increased undesirable effects.

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).

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

The use of Lasix can produce positive results in doping tests. In addition, the abuse of Lasix as a doping agent can endanger health.

Note on specific excipients
Lasix 20 mg or 40 mg solution for injection and Lasix 250 mg solution for infusion contain sodium, but less than 1 mmol (23 mg) sodium per ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

The simultaneous use of furosemide and glucocorticoids, carbenoxolone or laxatives can lead to increased potassium depletion with the risk of hypokalaemia developing. In this respect, large amounts of liquorice act like carbenoxolone.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin and acetylsalicylic acid) can attenuate the effect of furosemide. In patients who develop hypovolaemia during furosemide therapy or in dehydration, the simultaneous administration of nonsteroidal anti-inflammatory agents can trigger acute renal failure.

Probenecid, methotrexate and other medicinal products which, like furosemide, are secreted in considerable amounts in the tubules of the kidneys can attenuate the effect of furosemide.

An attenuation of the effect of furosemide has been described when phenytoin is administered concomitantly.

If furosemide is administered at the same time as cardiac glycosides, it should be borne in mind that in hypokalaemia and/or hypomagnesaemia developing during furosemide therapy, the sensitivity of the myocardium to cardiac glycosides is increased. There is a greater risk of ventricular arrhythmias (including torsades de pointes) if furosemide and medicinal products that can cause a syndrome of the prolonged QT interval (e.g. terfenadine, some class I and III antiarrhythmic agents) are used concomitantly in the presence of electrolyte disturbances.

The toxicity of salicylates in high doses can be potentiated if these medicinal products are used at the same time as furosemide.

Furosemide can potentiate the harmful effects of nephrotoxic medicinal products (e.g. antibiotics such as aminoglycosides, cephalosporins, polymyxins).

There may be a deterioration in renal function in patients who are treated concomitantly with furosemide and high doses of certain cephalosporins.

The ototoxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ototoxic medicinal products can be increased by the simultaneous administration of furosemide. Any hearing disorders that occur may be irreversible. The simultaneous use of the above mentioned medicinal products should therefore be avoided.

If cisplatin and furosemide are administered simultaneously, there is a possibility that hearing damage may occur. If, during cisplatin treatment, forced diuresis with furosemide is attempted, furosemide may only be used in a low dose (e.g. 40 mg with normal renal function) and when there is a positive fluid balance. If not, potentiation of the nephrotoxicity of cisplatin may result.

The concomitant administration of furosemide and lithium leads, via reduced lithium excretion, to an increase in the cardio- and neurotoxic effect of the lithium. It is therefore advisable to monitor carefully the plasma lithium level in patients who receive this combination.

If other antihypertensive agents, diuretics or medicinal products with blood-pressure-lowering potential are used at the same time as furosemide, a marked fall in blood pressure is to be expected. Severe falls in blood pressure or even shock and a deterioration in renal function (in isolated cases acute renal failure) have been observed, particularly when an ACE inhibitor or angiotensin-II-receptor antagonist has been administered for the first time or for the first time in a relatively high dose. If possible, the furosemide therapy should therefore be temporarily discontinued, or at least the dose should be reduced for three days before treatment with an ACE inhibitor or angiotensin-II-receptor antagonist is started or its dose increased.

Furosemide can reduce the renal elimination of probenecid, methotrexate and other medicinal products which, like furosemide, are secreted in considerable amounts in the tubules of the kidneys. In high-dose treatment (especially with both furosemide and the other medicinal product), this can lead to raised serum levels and a greater risk of undesirable effects due to furosemide or the concomitant medication.

The effect of theophylline or curare-type muscle relaxants may be increased by furosemide.
The effect of antidiabetic agents or hypertensive sympathomimetics (e.g. epinephrine, norepinephrine) may be attenuated if furosemide is used at the same time.

In patients treated with 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 regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.)

Other interactions
The concomitant administration of cyclosporin A and furosemide is associated with an increased risk of gouty arthritis as a result of hyperuricaemia caused by furosemide and impairment, by cyclosporin, of renal uric acid excretion.

In patients who were at high risk of renal damage due to X-ray contrast media and were treated with furosemide, a deterioration in renal function occurred more frequently after a contrast examination than in at-risk patients who received only an intravenous supply of fluid (hydration) before the contrast examination.

After the intravenous administration of furosemide within 24 hours of taking chloralhydrate, a sensation of heat, outbreaks of sweating, restlessness, nausea, a rise in blood pressure, and tachycardia may be experienced in isolated cases. The simultaneous use of furosemide and chloralhydrate should therefore be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
Furosemide should only be used in pregnancy for short periods and after very carefully weighing expected benefits against possible risks because it crosses the placenta.

Diuretics are not suitable for the routine treatment of hypertension and oedemas in pregnancy, since they impair the perfusion of the placenta and therefore intrauterine growth.

If however furosemide has to be given in maternal heart failure or renal

insufficiency, electrolytes and haematocrit as well as the growth of the fetus must be monitored precisely. Displacement of the bilirubin from the albumin binding, constituting an increased risk of kernicterus in hyperbilirubinaemia, has been discussed in relation to furosemide.

Furosemide crosses the placenta and reaches 100% of the maternal serum concentration in cord blood. No deformities in humans, which could be associated with exposure to furosemide, have been reported to date. There is however insufficient data available to make a final assessment of a possible damaging effect on the embryo/fetus. Urine production by the fetus in utero may be stimulated. In the treatment of premature infants with furosemide, the occurrence of urolithiasis has been observed.

Breastfeeding

Furosemide is excreted in the breast milk and inhibits lactation. Women should therefore not be treated with furosemide if they are breastfeeding. If necessary, they should cease breastfeeding (see also section 4.3).

4.7 Effects on ability to drive and use machines

Even when used correctly, this medicinal product can affect reaction to such an extent that the ability to drive, use machines or work without a safety rail or a safe foothold may be impaired. This applies particularly at the start of treatment, when increasing the dose or switching to another preparation or when taking the drug in combination with alcohol.

4.8 Undesirable effects

The following frequency ratings have been used as a basis for assessing undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

The frequency ratings for undesirable effects are based on literature data and relate to studies in which a total of 1,387 patients were treated with various dosages of furosemide in various indications.

Blood and lymphatic system disorders:

Common: haemoconcentration (if diuresis is excessive).

Uncommon: thrombocytopenia.

Rare: eosinophilia, leukopenia.

Very rare: haemolytic anaemia, aplastic anaemia, agranulocytosis.

Signs of agranulocytosis may be fever with chills, mucosal changes and sore throat.

Immune system disorders:

Uncommon: mucocutaneous reactions (see "Skin and subcutaneous tissue disorders").

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

Initial signs of shock include skin reactions, such as flushing or urticaria, restlessness, headache, sweating, nausea, cyanosis.

Not known: exacerbation or activation of systemic lupus erythematosus.

Metabolism and nutrition disorders (see section 4.4):

Very common: electrolyte disturbances (including symptomatic), dehydration and hypovolaemia (especially in elderly patients), elevated blood triglycerides.

Common: hyponatraemia and hypochloraemia (especially if sodium chloride intake is restricted), hypokalaemia (especially if potassium intake is concurrently reduced and/or in patients with increased potassium losses, e.g. in vomiting or chronic diarrhoea); blood cholesterol increased, blood uric acid increased and gout flare.

Uncommon: glucose tolerance decreased and hyperglycaemia. In patients with manifest diabetes, this can lead to a worsening of the metabolic status. Latent diabetes may become manifest (see section 4.4).

Not known: hypocalcaemia, hypomagnesaemia, metabolic alkalosis, Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

Commonly observed symptoms of hyponatraemia are apathy, calf cramps, anorexia, asthenia, drowsiness, vomiting and confusion.

Hypokalaemia can manifest as neuromuscular (muscle weakness, paraesthesia, paresis), intestinal (vomiting, constipation, meteorism), renal (polyuria, polydipsia) and cardiac symptoms (impulse formation and conduction disturbances). Severe potassium losses can lead to paralytic ileus or impaired consciousness and even coma.

Hypocalcaemia can induce tetany in rare cases.

As a result of hypomagnesaemia, tetany or occurrence of cardiac arrhythmias has been observed in rare cases.

Nervous system disorders:

Common: hepatic encephalopathy in patients with hepatic insufficiency (see section 4.3).

Rare: paraesthesias.

Ear and labyrinth disorders:

Uncommon: hearing disorders, mostly reversible, especially in patients with renal insufficiency or hypoproteinaemia (e.g. in cases of nephrotic syndrome) and/or when intravenous injections are too rapid. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.

Rare: tinnitus.

Vascular disorders:

Very common (with intravenous infusions): hypotension including orthostatic syndrome (see section 4.4).

Rare: vasculitis.

Not known: thrombosis (especially in elderly patients).

If diuresis is excessive, circulatory complaints (including circulatory collapse) can occur, especially in elderly patients and children, which mainly manifest as headache, dizziness, visual disturbances, dry mouth and thirst, hypotension and orthostatic dysregulation.

Gastrointestinal disorders:

Uncommon: nausea.

Rare: vomiting, diarrhoea.

Very rare: acute pancreatitis.

Hepatobiliary disorders:

Very rare: intrahepatic cholestasis, transaminases increased.

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, urticaria, rashes, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity.

Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS).

Renal and urinary disorders:

Very common: blood creatinine increased.

Common: urine volume increased.

Rare: tubulointerstitial nephritis.

Not known: urine sodium increased, urine chloride increased, blood urea increased, symptoms of urinary obstruction (e.g. in patients with prostatic hypertrophy, hydronephrosis, ureteric stenosis) and even urinary retention with secondary complications (see section 4.4), nephrocalcinosis and/or nephrolithiasis in preterm infants (see see section 4.4), renal failure (see section 4.5).

Congenital, familial and genetic disorders:

Not known: increased risk of patent ductus arteriosus when preterm infants are treated with furosemide in the first weeks of life.

General disorders and administration site conditions:

Rare: fever.

Not known: after intramuscular injection, local reactions such as pain.

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

Bundesinstitut für Arzneimittel und Medizinprodukte

Abt. Pharmakovigilanz

Kurt-Georg-Kiesinger-Allee 3

D-53175 Bonn

Website: www.bfarm.de

4.9 Overdose

a) Symptoms of overdose

The clinical picture in acute or chronic overdose depends on the extent of water and electrolyte loss. Overdosage can lead to hypotension, orthostatic dysregulation, electrolyte disturbances (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. In more severe fluid depletion, pronounced hypovolaemia, dehydration, circulatory collapse and haemoconcentration with a tendency to thrombosis may occur. In rapid water and electrolyte losses, delirious states may be observed. In rare cases, anaphylactic shock (symptoms: sweating, nausea, cyanosis, severe fall in blood pressure, clouding of consciousness or even coma) may be encountered.

b) Therapeutic measures in overdose

In overdose or signs of hypovolaemia (hypotension, orthostatic dysregulation) treatment with Lasix must be discontinued immediately.

In addition to monitoring the vital signs, repeated checks on the water and electrolyte balance, the acid-base equilibrium, the blood sugar and the nitrogen-containing constituents of the urine must be carried out and any deviations corrected if necessary.

In patients with impaired micturition (e.g. those with prostatic hyperplasia) provision must be made for a free flow of urine, because a sudden flood of urine can lead to urinary retention with overextension of the bladder.

Treatment for hypovolaemia:

volume replacement

Treatment for hypokalaemia:

potassium replacement

Treatment for circulatory collapse:

supine position with legs raised, if necessary shock therapy

Emergency measures in the event of anaphylactic shock:

At the first signs (e.g. skin reactions such as urticaria or flushing, restlessness, headache, outbreaks of sweating, nausea, cyanosis):

- stop the injection/infusion, maintain venous access.
- as well as the usual emergency measures, place the patient in a supine position with the legs raised, keep the airways clear and give oxygen.
- if necessary, implement other intensive care emergency measures (including the administration of adrenaline (epinephrine), volume replacement fluids, glucocorticoids).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: high-ceiling diuretic

ATC Code: C03CA01

Furosemide is a potent, short- and fast-acting loop diuretic. By blocking the $Na^+/2Cl^-/K^+$ ion carrier, it inhibits the reabsorption of these ions in the ascending part of the loop of Henle. Fractional sodium excretion can constitute up to 35% of the sodium that has undergone glomerular filtration. As a result of the raised sodium excretion, there is increased urine excretion and a rise in K^+ secretion in the distal tubules as a secondary phenomenon due to osmotically bound water. Also raised is the excretion of Ca^{2+} and Mg^{2+} ions. In addition to the depletion of the above mentioned electrolytes, reduced excretion of uric acid and impairment of the acid-base balance towards metabolic alkalosis can result.

Furosemide interrupts the tubuloglomerular feedback mechanism in the macula densa so there is no attenuation of saluretic efficacy.

Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In heart failure, furosemide immediately brings about a reduction in the preload on the heart by dilating the venous capacitance vessels.

This early vascular effect appears to be mediated by prostaglandins and necessitates adequate renal function with activation of the renin-angiotensin-aldosterone system and intact prostaglandin synthesis.

Furosemide lowers the blood pressure as a result of increased sodium chloride excretion and a reduced response of the smooth vascular musculature to vasoconstrictor stimuli, and also because of a decrease in blood volume.

5.2 Pharmacokinetic properties

After intravenous administration of furosemide an onset of action can be expected within 2-15 minutes.

Plasma protein binding of furosemide is about 95%; it may be reduced in renal insufficiency by up to 10%. The relative volume of distribution is in the region of 0.2 l/kg body weight (in neonates 0.8 l/kg body weight).

Furosemide is metabolised in the liver to only a minor extent (about 10%) and is mostly excreted unchanged. Two-thirds of it is eliminated via the kidneys and one-third in the bile and faeces. In normal renal function the elimination half-life is about 1 hour; it may be extended to up to 24 hours in terminal renal failure.

5.3 Preclinical safety data

The acute oral toxicity was low in all the species tested. Chronic toxicity studies in rats and dogs gave rise to changes in the kidneys (including fibrosis and calcification of the kidneys).

In-vitro and in-vivo tests to investigate the genetic toxicology of furosemide gave no indication that might be of clinical relevance relating to a genotoxic potential.

Long-term studies in rats and mice showed no evidence of a carcinogenic potential.

In reproductive toxicology studies, following the administration of high doses, a reduced number of differentiated glomeruli, skeletal anomalies in the scapula, humerus and ribs (due to hypokalaemia) were observed in rat foetuses, as well as hydronephrosis in mouse and rabbit foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lasix 20 mg/40 mg solution for injection
Sodium chloride, sodium hydroxide, water for injection

Lasix 250 mg solution for infusion
Sodium hydroxide, mannitol (Ph.Eur.), water for injection

6.2 Incompatibilities

Injection solutions/infusion solutions which have an acid or weakly acid reaction and a pronounced buffering capacity in the acid range must not be mixed with Lasix solution for injection or infusion. With these mixtures, the pH is shifted into the acid range and the only slightly water-soluble furosemide precipitates out as a crystalline deposit.

6.3 Shelf life

Lasix 20 mg/40 mg solution for injection
3 years.

Lasix 250 mg solution for infusion
18 months.

The ready-to-use preparation was found to be physically and chemically stable for 24 hours at 25 °C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Brown glass ampoules

Lasix 20 mg solution for injection
Packs containing
4 ampoules of 2 ml each
50 ampoules of 2 ml each

Hospital pack containing
20 (4x5) ampoules of 2 ml each

Lasix 40 mg solution for injection
Pack containing
4 ampoules of 4 ml each

Hospital pack containing
20 (4x5) ampoules of 4 ml each

Lasix 250 mg solution for infusion
Pack containing
4 ampoules of 25 ml each
6 ampules of 25 ml each

Hospital pack containing
20 (4x5) ampoules of 25 ml each
24 (4x6) ampoules of 25 ml each

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Postal address:
Postfach 80 08 60
D-65908 Frankfurt am Main, Germany

Telephone: + 49 (0)1 80 2 22 20 10*
Fax: + 49 (0)1 80 2 22 20 11*
E-mail: medinfo.de@sanofi.com

8. MARKETING AUTHORISATION NUMBERS

Lasix 20 mg solution for injection:
6132084.00.00

Lasix 40 mg solution for injection:
35018.00.00

Lasix 250 mg solution for infusion:
6132115.00.00

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Lasix 20 mg solution for injection:
Date of first authorization: September 21, 1999
Date of last renewal of the authorization: October 04, 2006

Lasix 40 mg solution for injection:
Date of first authorization: February 28, 1996
Date of last renewal of the authorization: October 04, 2006

Lasix 250 mg solution for infusion:
Date of first authorization: September 21, 1999
Date of last renewal of the authorization: October 04, 2006

10. DATE OF REVISION OF THE TEXT

May 2015

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

* €0.06 /call (landline Germany); max. €0.42 /min (mobile)

Direct all enquiries to:
Rote Liste Service GmbH
SmPC Service
Postfach 11 01 71
D-10831 Berlin
Germany