SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Furosemide - Fresenius 20 mg/ 2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of furosemide.
Each 2 ml ampoule contains 20 mg of furosemide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for I.M or I.V injection
Clear, colorless to almost colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide is a potent diuretic indicated for use when a prompt and effective diuresis is required. Furosemide Injection 20mg/2ml is appropriate for use in emergencies or when oral therapy is not feasible.
The Indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and method of administration

Route of administration: intramuscular or intravenous use.

Adults: Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine > 5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

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

To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide infusion is generally to be preferred to repeated bolus injections. Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals (approximately four hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required, it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly: The dosage recommendations for adults apply, but in the elderly, furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

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

4.3 Contraindications

Furosemide is contraindicated under the following circumstances:

- Hypersensitivity to furosemide, sulphonamides or to any of the excipients
- Anuria
- Renal failure with anuria
- Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents
- Hepatic coma and precoma
- Severe hypokalaemia
- Severe hyponatraemia
- Hypovolaemia or dehydration
- In breast-feeding women

4.4 Special warnings and precautions for use

Particularly close medical supervision is required under the following circumstances:

- Hypotension - correct before use
- Manifest or latent diabetes mellitus (regular monitoring of the blood glucose levels)
- Gout (regular monitoring of the serum uric acid levels)
- Patients with hepatorenal syndrome
- Urinary flow obstruction (e.g., in prostatic hypertrophy, hydronephrosis, ureterostenosis)
- Hypoproteinaemia, e.g., in nephrotic syndrome (cautious dose titration)
- Liver cirrhosis and concurrent impairment of renal function
- Patients who would be at particular risk following a pronounced fall in blood pressure, e.g., patients with cerebrovascular insufficiency or coronary heart disease
- Premature infants (risk of development of nephrocalcinosis/nephrolithiasis; monitoring of renal function, nephrosonography)

In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life may increase the risk of persistence of patent *ductus arteriosus Botalli*.

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring.

In patients with micturition disorders (e.g., in prostatic hypertrophy), furosemide may only be administered if urinary flow is ensured, as any sudden flood of urine may cause ischuria with overextension of the bladder.

Steps should be taken to correct hypovolaemia before commencing therapy in oliguria.

Caution is required in patients with liver failure, porphyria, pancreatitis or a history of pancreatitis, systemic lupus erythematosus or a history of systemic lupus erythematosus or severe asthma (hypokalaemia associated with beta2-agonist therapy can be potentiated by the concurrent use of diuretics).

Furosemide leads to greater elimination of sodium and chloride and, consequently, of water. The elimination of other electrolytes (in particular potassium, calcium and magnesium) is also increased. As, in course of the therapy with Furosemide disturbances of the fluid and electrolyte levels are frequently observed as a result of the increased electrolyte elimination, regular controls of the serum electrolytes are indicated. First and foremost, during long-term therapy with Furosemidethe serum electrolytes (particularly potassium, sodium and calcium), bicarbonate, creatinine, urea and uric acid as well as the

blood glucose level should be monitored at regular intervals.
Particularly close monitoring is required in patients at increased risk of developing electrolyte disturbances or in cases of significant additional fluid loss (e.g., due to vomiting, diarrhoea or intense sweating). Hypovolaemia or dehydration as well as any significant serum electrolyte or acid-base balance disturbances must be corrected. This may require temporary discontinuation of treatment with furosemide.
The possible development of electrolyte disturbances is influenced by underlying diseases (e.g., hepatic cirrhosis, cardiac insufficiency), accompanying medication (see section 4.5) and nutrition.
The weight loss due to increased diuresis should not exceed 1 kg/day, regardless of the extent of urinary excretion.
In patients with nephrotic syndrome, dosing must be cautious due to the risk of increased undesirable effects.
Prolonged treatment with furosemide can lead to thiamine deficiency, particularly in congestive heart failure or the elderly.
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.

Concurrent administration with Risperidone:

In placebo-controlled studies with risperidone carried out in elderly patients with dementia, higher mortality incidence was observed in patients treated concomitantly with furosemide and risperidone (7.3 %, average age 79, age range 75 to 97), as compared to patients treated with risperidone only (3.1 %, average age 80, age range 67 to 90) or with furosemide only (4.1 %, average age 84, age range 70 to 96). The concomitant administration of risperidone with other diuretics (first and foremost low-dose thiazide diuretics) was not associated with a similar finding.
No pathophysiological mechanism for the explanation of this observation could be identified and no uniform mortality pattern could be determined. Nonetheless, caution is indicated and the risks and benefits of this combination or of the simultaneous therapy with another potent diuretic must be weighed prior to making a therapeutic decision. In patients having received other diuretics as accompanying therapy together with risperidone, the mortality incidence was not increased.
Irrespective of the therapy, dehydration was a general risk factor for mortality and it should therefore be avoided in elderly patients with dementia.
Exacerbation or activation of systemic lupus erythematosus is possible.

Effects in misuse for doping purposes

Use of Furosemide for doping purposes can lead to positive results in doping controls. Use of Furosemide as doping agent can result in health damage.
Furosemide contains sodium, but less than 1 mmol (23 mg) sodium per ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced hypotensive effect. Orthostatic hypotension, associated with diuretics, may be enhanced.
Aldesleukin: Enhanced hypotensive effect.
Anaesthetics, general: Enhanced hypotensive effects.
Anion-exchange resins: Colestyramine and colestipol markedly reduce the absorption of furosemide. Administer two to three hours apart.
Concurrent administration of furosemide and glucocorticoids, carbenoxolone or laxatives may cause increased potassium loss. In this regard, liquorice has the same effect as carbenoxolone.
Corticosteroids: The increased risk of hypokalaemia occurs particularly with the naturally occurring corticosteroids such as cortisone and hydrocortisone. The synthetic corticosteroids have a much less marked potassium-losing effect. Fluid retention associated with corticosteroid use may cause antagonism of diuretic/antihypertensive effect. Concomitant administration of corticosteroids may cause sodium retention.
Non-steroidal anti-inflammatory drugs (e.g., indomethacin, ketorolac and acetylsalicylic acid) may attenuate the effect of furosemide. In patients who develop hypovolaemia under furosemide therapy or in patients with dehydration, concurrent administration of non-steroidal anti-inflammatory drugs may cause acute renal failure.
Probenecid, methotrexate and other drugs which, like furosemide, undergo considerable renal tubular secretion, may attenuate the effect of furosemide.
Antiepileptics: Increased risk of hyponatraemia with concomitant carbamazepine.
Attenuation of the effect of furosemide has been reported following concurrent administration of phenytoin.
As sucralfate reduces absorption of furosemide and thus attenuates its effect, an interval of at least 2 hours should be allowed between administration of these two drugs.
Anxiolytics and hypnotics: Administration of chloral hydrate followed by intravenous furosemide may result in a syndrome of hot flushes, sweating, tachycardia and hypertension.

If there is concurrent administration of cardiac glycosides, it should be borne in mind that in patients developing hypokalaemia and/or hypomagnesaemia during furosemide therapy, myocardial sensitivity to cardiac glycosides is enhanced.

There is an increased risk of ventricular arrhythmias (including torsade de pointes) if there is concurrent administration of drugs which may induce QT interval prolongation syndrome (e.g., terfenadine, some class I and III antiarrhythmic agents) in the presence of disturbances of serum electrolytes.

The toxicity of high dosed salicylates may be enhanced by concurrent administration of furosemide.

Furosemide may enhance the toxic effects of nephrotoxic antibiotics (e.g., aminoglycosides, cephalosporins, polymyxins).

The ototoxicity of aminoglycosides (e.g., kanamycin, gentamicin, tobramycin), vancomycin and other ototoxic drugs may be enhanced by concurrent administration of furosemide. Any hearing disorders which occur may be irreversible. Concurrent administration of the above drugs should therefore be avoided.

Antifungals: Increased risk of hypokalaemia with loop diuretics and amphotericin.

Anticoagulants: Reduced anticoagulant effect when furosemide used concomitantly with warfarin.

Anti-arrhythmics: Toxicity of amiodarone, disopyramide, flecainide and quinidine is increased if hypokalaemia occurs. Action of lidocaine and mexiletine is antagonised by hypokalaemia.

Hypokalaemia increases risk of ventricular arrhythmias with sotalol, a beta-blocker.

Concurrent administration of cisplatin and furosemide is likely to result in hearing damage. If accelerated diuresis with furosemide is intended during cisplatin treatment, furosemide may only be administered at a low dose (e.g., 40 mg with normal renal function) and if there is a positive fluid balance. Otherwise, the nephrotoxicity of cisplatin may be enhanced.

Concurrent administration of furosemide and lithium reduces lithium elimination, which enhances the cardiotoxic and neurotoxic effect of lithium. Close monitoring of plasma lithium levels is therefore recommended in patients receiving this combination.

If other antihypertensive agents, diuretics or drugs with hypotensive potential are administered concomitantly with furosemide, an increased hypertensive effect is to be expected.

Diuretics: Increased risk of hypokalaemia with other loop diuretics and other diuretics, including acetazolamide and thiazides. Severe electrolyte disturbances may occur in patients given metolazone concurrently with furosemide. The dosage of concurrently administered diuretics may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.

Antihypertensives: Furosemide enhances the hypotensive action of other antihypertensive drugs, including beta-blockers, calcium-channel blockers and hydralazine. The dosage of currently administered antihypertensive agents may require adjustment. There is an increased risk of first-dose hypotension with alpha blockers such as prazosin or angiotensin-converting enzyme (ACE) inhibitors such as captopril. Particular care should be taken with ACE inhibitors and angiotensin II antagonists when initiating or increasing their dose in concomitant therapy with furosemide, since combination can result in marked reduction in blood pressure and deterioration in renal function. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating or increasing the dose of an ACE inhibitor or angiotensin II receptor antagonist. Long-term intensive treatment with captopril can enhance the natriuretic response to furosemide.

Furosemide may reduce the renal elimination of probenecid, methotrexate and other drugs which, like furosemide, undergo considerable renal tubular secretion. High-dose treatment (particularly both with furosemide and the other drug) may cause elevated serum levels and an increased risk of undesirable effects due to furosemide or the concomitant medication.

The effect of theophylline or curare-like muscle relaxants may be enhanced by furosemide.

The effects of anti-diabetics or pressor amines (e.g., epinephrine, norepinephrine) may be attenuated by concurrent administration of furosemide.

Antipsychotics: Hypokalaemia increases risk of ventricular arrhythmias with primozide and sertindole, concurrent use should be avoided. Enhanced hypotensive effect with phenothiazines.

In patients treated with risperidone, caution is indicated and the risks and benefits of this combination or of the simultaneous therapy with another potent diuretic must be weighted (see section 4.4 on the increased mortality in elderly patients with dementia concurrently treated with risperidone).

Antidepressants: Increased risk of postural hypotension with tricyclic antidepressants. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Increased risk of hypokalaemia when furosemide and reboxetine are used concomitantly.

Antidiabetics: The hypoglycaemic effect is antagonised by loop diuretics.

Dompaminergics: Enhanced hypotensive effect with levodopa.

Laxatives: Prolonged use may increase the risk of developing hypokalaemia.

Muscle relaxants: Enhanced hypotensive effect may occur with tizanidine; effects of curare-type muscle relaxants may be potentiated.

Nicotine: Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide.

Nitrates: Enhanced hypotensive effect.

Prostaglandins: Hypotensive effect may be potentiated by alprostadil.

Sympathomimetics: There is an increased risk of hypokalaemia with high doses of β2-sympathomimetics. Effects of pressor amines may be attenuated.
Ulcer healing drugs: Carbenoxolone and liquorice may increase risk of hypokalaemia. Fluid retention associated with carbenoxolone may cause antagonism of diuretic/antihypertensive effect. Ranitidine causes a moderate increase in the bioavailability of furosemide.

Other forms of interaction

Concomitant administration of ciclosporin A and furosemide is connected with an increased risk of Arthritis urica, as a result of the furosemide-caused hyperuricemia and of the impairment of the renal urine excretion by ciclosporin.
In patients with high risk of renal impairment caused by X-ray contrast substances, deterioration of the renal function under furosemide treatment occurred more frequently after X-ray contrast examination than in high-risk patients that have undergone hydration only prior to the contrast examination.
In isolated cases, following intravenous administration of furosemide within 24 hours of chloral hydrate intake, hot flushes, sweating, agitation, nausea, a rise in blood pressure and tachycardia may occur. Concurrent administration of furosemide and chloral hydrate must therefore be avoided.

4.6 Pregnancy and lactation

Pregnancy

During pregnancy, furosemide may only be administered on a short-term basis and if there are very compelling medical reasons, as furosemide crosses the placental barrier.
Diuretics are not suitable for routine therapy of hypertension and oedema during pregnancy, as they impair placental perfusion and hence intrauterine growth.
If furosemide administration is required to treat cardiac or renal insufficiency in a pregnant woman, electrolyte and haematocrit values and foetal growth must be closely monitored.
Displacement of bilirubin from the albumin binding and hence an increased risk of kernicterus in hyperbilirubinaemia is discussed for furosemide.
Furosemide crosses the placental barrier and in the cord blood the agent reaches 100 % of the maternal serum concentration. To date, no malformations associated with furosemide exposure have been reported in humans. There has been insufficient experience, however, to allow any final conclusions to be drawn about any potentially

damaging effect on the embryo/foetus. *In utero* foetal urine production may be stimulated. Following treatment of premature infants with furosemide, urolithiasis has been observed.

Lactation

Furosemide is excreted into the breast milk and inhibits lactation. Nursing mothers may therefore not be treated with furosemide. If necessary, the infant should be weaned (see section 4.3).

4.7 Effects on ability to drive and use machines

Furosemide has a low effect on the ability to drive and to operate machinery. Even if administered correctly, this drug can impair responsiveness so that the ability to drive a vehicle, or operate machinery may be impaired. This effect is more pronounced at the beginning of treatment, if the dose is increased and in combination with alcohol.

4.8 Undesirable effects

The following frequency conventions are used in the rating of undesirable effects:

Very common	≥ *1/10*
Common	≥ *1/100 to < 1/10*
Occasional	≥ *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 diseases

Common:	Haemoconcentration (in excessive diuresis)
Occasional:	Thrombocytopenia
Rare:	Eosinophilia, leukopenia
Very rare:	Haemolytic anaemia, aplastic anaemia, agranulocytosis.

Indications of agranulocytosis can be fever and shivers, changes in the mucosa and throat ache.

Immune system diseases

Occasional:	Allergic skin and mucosa diseases (see "Skin and subcutaneous tissue diseases").
Rare:	Severe anaphylactic or anaphylactoid reactions such as anaphylactic shock (for treatment see section 4.9).
Unknown:	Exacerbation or activation of systemic lupus erythematosus.

Metabolism and nutrition diseases

Very common:	Electrolyte disorders (including symptomatic), dehydration and hypovolemia (in particular in elderly), elevated triglycerides in the blood.
Common:	Hyponatremia and hypochloraemia (especially in restricted sodium chloride supply), hypokalaemia (especially in simultaneously restricted potassium supply and/or increased potassium losses, e.g., in vomiting and diarrhea); elevated blood cholesterol, uric acid in the blood and gout attacks.
Occasional:	Reduced glucose tolerance and hyperglycemia. In patients with manifest Diabetes mellitus, a deterioration of the metabolism can result. Latent Diabetes mellitus can become manifest.
Unknown:	Hypocalcaemia, hypomagnesaemia, metabolic alkalosis, pseudo-Bartter syndrome (in connection with abuse and/ or long-term use of furosemide.
Very rare:	Haemolytic anaemia, aplastic anaemia, agranulocytosis.

Frequently observed symptoms of hyponatraemia are apathy, lower leg spasms, lack of appetite, weakness sensation, somnolence, vomiting and confusion states.

Hypokalaemia may occur due to increased renal potassium loss, particularly as a result of a concurrently reduced potassium intake and/or increased extrarenal potassium loss (e.g., due to vomiting or chronic diarrhoea). Hypokalaemia is characterised by neuromuscular symptoms (amyosthenia, paraethesia, pareses), intestinal symptoms (vomiting, obstipation, meteorism), renal symptoms (polyuria, polydipsia) and cardiac symptoms (impulse generation and conduction disorders). Severe potassium loss can lead to paralytic ileus or unconsciousness, sometimes including coma.

Increased renal magnesium loss can cause hypomagnesaemia, resulting, in rare cases, in tetany or cardiac arrhythmia.

Nervous system disorders

Common:	Hepatic encephalopathy in patients with liver insufficiency (see section 4.3).
Rare:	Paraesthesia
Unknown:	Vertigo, fainting and loss of consciousness (caused by symptomatic hypotonia).

Ear and labyrinth diseases

Occasional:	Hearing disorders, mostly reversible, in particular in patients with renal insufficiency or hypoproteinaemia (e.g., in nephritic syndrome) and/or in too rapidly administrated intravenous injection. Deafness (sometimes irreversible).
Rare:	Tinnitus

Vascular diseases

Very common:	In intravenous infusion, hypotension, including orthostasis syndrome (see section 4.4).
Rare:	Vasculitis
Unknown:	Thrombosis

Excessive diuresis may lead to circulatory problems, particularly in elderly patients and children, mainly characterised by headache, vertigo, vision disorders, dry mouth and thirst, hypotension and orthostatic regulatory disorders.

Gastrointestinal diseases

Occasional:	Nausea
Rare:	Vomiting, diarrhoea
Very rare:	Acute pancreatitis

Hepatobiliary diseases

Very rare:	Intrahepatic cholestasis, elevated transaminases.

Skin and subcutaneous tissue diseases

Uncommon:	Pruritus, urticarial, rashes, bullous dermatitis, Erythema multiforme, pemphigoid, Dermatitis exfoliativa, photosensitivity.
Unknown:	Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug exanthema with eosinophilia and systemic symptoms (DRESS).

Renal and urinary diseases

Very common:	Elevated blood creatinine
Common	Increased urine volume
Rare:	Elevated urine sodium, elevated urine potassium, elevated blood urea, symptoms of urinary flow impairment (e.g., in patients with prostate hypertrophy, hydronephrosis, ureter stenosis) up to urinary retention with secondary complication (see section 4.4), nephrocalcinosis and/or nephrolithiasis in

	the newborn (see section 4.4), renal failure (see section 4.4).

Pregnancy, puerperium and perinatal conditions

Unknown:	Premature infants may develop nephrolithiasis and/or nephrocalcinosis. In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life may increase the risk of persistence of patent ductus arteriosus Botalli.

General disorders and administration site conditions

Rare:	Fever
Unknown:	Following intramuscular injection, local reactions such as pain may occur.

Other effects: Thiamine deficiency with prolonged treatment, particularly in congestive heart failure and the elderly.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

Symptoms:

The clinical picture in acute or chronic overdose depends upon the extent of the electrolyte and fluid loss. Overdose can cause hypotension, orthostatic regulatory disorders, electrolyte imbalance (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. Severe fluid loss can lead to pronounced hypovolaemia, dehydration, circulatory failure and haemoconcentration with a tendency to thrombosis. In patients with rapid fluid and electrolyte loss, delirious states may occur. Rarely, anaphylactic shock has been observed (symptoms: attack of sweating, nausea, cyanosis, severe drop in blood pressure and disturbance of consciousness, sometimes including coma and others).

Treatment:

In the event of overdose or signs of hypovolaemia (hypotension, orthostatic regulation disorders), treatment with Furosemide must be discontinued immediately.
In addition to the monitoring of the vital signs, repeated checks must be made of the fluid and electrolyte balance, acid-base balance, blood glucose and the substances obligatory excreted by urine, and any necessary corrections made.
In patients with micturition disorders (e.g., in prostate hypertrophy), urinary flow must be ensured, as any sudden flood of urine may cause ischuria with overextension of the bladder.
Therapy in patients with hypovolaemia: volume replacement
Therapy in patients with hypokalaemia: potassium replacement
Therapy in patients with circulatory failure: passive leg-raising, if required shock therapy

Immediate measures in the treatment of anaphylactic shock:
At the first signs (e.g., cutaneous reactions such as urticaria or flush, agitation, headache, attack of sweating, nausea, cyanosis):

- Discontinue the injection, leave the venous access.
- Besides other common emergency measures Trendelenburg position, maintain the airways, oxygen administration!
- If required, further measures, in intensive care if necessary (including epinephrine administration, volume replacement agents, glucocorticoid) should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: potent diuretic

ATC code: C03CA01

Furosemide is a potent, short-acting loop diuretic with a rapid action. By blocking the Na+/2Cl-/ K+ ion carriers in the ascending limb of the Henle loop, it inhibits the reabsorption of these ions. The fractional sodium excretion can be up to 35 % of the sodium filtered by the glomerulus. As a result of increased sodium excretion, a secondary effect, due to osmotically bound water, occurs, i.e. increased diuresis and an increase in distal-tubular K+ secretion. The excretion of Ca2+ and Mg2+ ions is also increased. In addition to the loss of the above named electrolytes, reduced excretion of uric acid and disturbances of the acid-base balance, tending to metabolic alkalosis, may also occur.
Furosemide interferes with the tubuloglomerular feedback mechanism at the macula densa, so that there is no attenuation of the saluretic efficacy.
Furosemide causes dose-dependent stimulation of the renin-angiotensin-aldosterone system.
In patients with cardiac insufficiency, furosemide causes an acute reduction in cardiac preload by dilation of the venous capacity vessels. This early vascular effect appears to be mediated by prostaglandins and requires a sufficient renal function with activation of the renin-angiotensin-aldosterone system and an intact prostaglandin synthesis.
Furosemide has an antihypertensive effect due to increased sodium chloride excretion, a reduced responsiveness of the smooth vascular muscles to vasoconstrictive stimuli and a decrease in blood volume.

5.2 Pharmacokinetic properties

Following intravenous furosemide administration, onset of action can be expected within 2-15 minutes.
Furosemide is approximately 95 % plasma protein-bound. In renal insufficiency, this may be reduced by up to 10 %. The relative volume of distribution is 0.2 l/kg BW (in neonates 0.8 l/kg BW).
Furosemide is only slightly metabolised in the liver (approximately 10 %) and is mainly excreted unchanged. Elimination is two thirds renal and one third in the bile and faeces.

If renal function is normal, the elimination half-life is approximately 1 hour. In terminal renal insufficiency it can be prolonged to up to 24 hours.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Sodium hydroxide, Water for injections.

6.2 Incompatibilities

It must be ensured that the pH value of the reconstituted solution for injection is in the weak alkaline to neutral range (pH value not less than 7). Acidic solutions must not be used, as the active ingredient may precipitate.
Solutions for injection with an acidic or weakly acidic reaction and having a marked buffer capacity in the acidic range may not be mixed with Furosemide. In such mixtures, the pH value is displaced into the acid range and the slightly soluble furosemide precipitates out as crystalline precipitate.

6.3 Special precautions for storage

Store below 25°C.
Keep the ampules in the outer carton in order to protect from light.
For single use only. Once opened the product should be used immediately.

6.4 Nature and contents of container

Amber glass ampoule of hydrolytic class I.
5 x 2 ml, 10 x 2 ml, 50 x 2 ml, 100 x 2 ml.
Not all pack sizes may be marketed.

6.5 Special precautions for disposal and other handling

Furosemide can be mixed or diluted with 0.9% sodium chloride or Ringer's lactate solutions.
After dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C 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.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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9. REGISTRATION NUMBER

158-15-34680-00

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