Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Furosemide 40 mg tablets

Active substance: furosemide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 40 mg furosemide.

Excipient: 61,8 mg lactose

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet

White, round tablet, lightly convex with one sided score notch

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
1) Treatment of oedema associated with
   - cardiac disease
   - liver disease
   - renal disease including nephrotic syndrome; in patients with nephrotic syndrome, therapy of the underlying disorder has priority.

   Treatment of pulmonary oedema.
2) Arterial hypertension

4.2 Posology and Method of Administration

The usual initial adult dose is 20−40 mg daily; however the dose may need adjusting on an individual basis until an effective dose is achieved.
The subsequent dosage guidelines apply to adults:

Hypertension
The usual dose is 40 mg furosemide once daily.
In severe cases up to 60 mg furosemide per day. In case of insufficient response combination with non-diuretic anti-hypertensives is recommended.

Oedema associated with cardiac or hepatic diseases
The usual initial dose in adults is 20−40 mg furosemide. If the diuretic response is not satisfactory, the single dose can be doubled to 80 mg furosemide after 6 hours. If there is still inadequate diuresis, an additional dose of 160 mg furosemide can be given after a further 6 hours.

The daily maintenance dose is usually 40−80 mg furosemide.

Oedema associated with renal diseases
The usual initial dose in adults is 40 mg furosemide. If the diuretic response is not satisfactory, the single dose can be doubled to 80 mg furosemide after 6 hours. If there is still inadequate diuresis, an additional dose of 160 mg furosemide can be given after a further 6 hours.

The daily maintenance dose is usually 40−80 mg furosemide.

A higher dose (IV administration) may be required in patients with renal insufficiency.
In patients with nephrotic syndrome, the dosage must be determined with caution, because of the risk of a higher incidence of adverse reactions.

Children
The usual initial dose for oral furosemide in infants and children is 2 mg/kg body weight given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6 to 8 hours after the previous dose (maximum of 40 mg daily).

Elderly
The dosage recommendations for adults apply. In general furosemide is eliminated more slowly in elderly patients; the dose should be titrated until a satisfactory response is achieved.

In case of renal insufficiency less furosemide will reach the renal tubules.
An increase of dose may be necessary to obtain the same diuretic effect.

No dosage adjustment is needed for patients with mild hepatic impairment; however the dosage may require adjustment in cases of moderate to severe hepatic impairment.

Method and duration of administration
For oral administration.

It is recommended that Furosemid 40 mg tablets are taken on an empty stomach, and with plenty of liquid.

4.3 Contraindications
- hypersensitivity to the active substance, sulphonamides or to any of the excipients
- renal failure with anuria
- coma and precoma hepaticum
- severe hypokalaemia
- severe hyponatraemia
- hypovolaemia or dehydration
- breast-feeding women

4.4. Special warnings and precautions for use
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.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Particularly careful monitoring is necessary in:
- patients with hypotension.
- patients who are at risk from a pronounced fall in blood pressure.
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase (regular monitoring of blood glucose values)
- patients with gout (regular monitoring of uric acid in serum)
- patients with hepatorenal syndrome.
- patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- premature infants (possible development of nephrocalcinosis / nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

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

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).

Caution should be observed in patients liable to electrolyte deficiency. Regular monitoring of serum sodium, potassium, calcium, bicarbonate, uric acid, blood glucose level and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

During long term treatment with furosemide, a potassium rich diet is always indicated (e.g. potatoes, bananas, tomatoes, spinach, dry fruits). Sometimes a medicinal substitution of potassium is recommended. In other cases (i.e. liver cirrhosis), it is indicated to prevent hypokaliaemia and metabolic alkalosis by administering a potassium sparing agent.

In case of renal insufficiency less furosemide will reach the renal tubules. An increase of dose may be necessary to obtain the same diuretic effect.

The duration of administration depends on the nature and the severity of the disease.

Use of furosemide can lead to positive results in doping tests. Improper use of the medicinal product furosemide for doping purposes can jeopardize health.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of other medicinal products on furosemide
Certain **non-steroidal anti-inflammatory agents** (e.g. indometacin, acetylsalicylic acid) may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.

Effect of furosemide on other medicinal products
Cardiac glycosides
In concurrent treatment with cardiac glycosides, it should be taken into account that if hypokalaemia and/or hypomagnesaemia develop during therapy with furosemide, the sensitivity of the myocardium towards cardiac glycosides is increased. There is an increased risk of ventricular arrhythmias (including torsades de pointes) when medicinal products that may cause prolongation of the QT interval (e.g. terfenadine, some antiarrhythmics of classes I and III) are used concomitantly, and in the presence of electrolyte imbalance.

In patients concomitantly treated with furosemide and high doses of certain cephalosporins, renal function can exacerbate.

Anti-hypertensive agents
The dosage of concurrently administered antihypertensive agents may require adjustment.

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

Nephrotoxic antibiotics
The toxic effects of nephrotoxic antibiotics (e.g. aminoglycosides, cephalosporins, polymyxins) may be increased by concomitant administration of potent diuretics such as furosemide.

Ototoxic antibiotics
Furosemide may potentiate the ototoxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ototoxic medicinal products. Since this may lead to irreversible damage, these medicinal products must only be used with furosemide if there are compelling medical reasons.

Non-steroidal anti-inflammatory agents
Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

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

Others:
Oral furosemide and **sucralfate** must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Furosemide may sometimes attenuate the effects of other products (e.g. the effects of **anti-diabetics** and of **pressor amines**) and sometimes potentiate them (e.g. the effects of **salicylates, theophylline** and **curare-type muscle relaxants**).

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.

Attenuation of the effect of furosemide may occur following concurrent administration of **phenytoin**.

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

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, Beta-2-sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

Probenecid, methotrexate and other products which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide.

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

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Furosemide should not be used during pregnancy unless clearly necessary (for example such as in the case of maternal congestive heart failure). Furosemide crosses placental barrier and can therefore cause increased diuresis of the foetus.

Furosemide passes the placenta and reaches 100% of the maternal serum concentration in cord blood. No malformationsin humans which might be associated withexposure furosemidehave been reported to date.However, there is insufficient experience to allow a concluding evaluation of a potential damaging effect in the embryo/foetus.Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
In utero urinary production can be stimulated in the foetus. Urolithiasis has been observed after treatment of premature infants with furosemide.

In pregnancy furosemide should only be used on advice of a physician and should only be used if the oedema is not related to the pregnancy. Treatment of oedema and hypertension caused by pregnancy with diuretics is not advisable in general as the physiological hypovolaemia may be enhanced and the placental perfusion may be lowered. Treatment during pregnancy requires monitoring of foetal growth.
If use of furosemide is essential for the treatment of cardiac or renal insufficiency during pregnancy, careful monitoring of electrolytes, haematocrit and foetal growth is essential. Possible displacement of bilirubin from the albumin binding and thus elevated risk of nuclear icterus in hyperbilirubinaemia is discussed for furosemide.

Lactation

Furosemide passes into breast milk and may inhibit lactation. Women must therefore not be treated with furosemide when breast-feeding. If necessary, breastfeeding is to be discontinued (see also section 4.3).

4.7 Effects on ability to drive and use machines

Furosemide has minor or moderate influence on the ability to drive and use machines. It may reduce mental alertness.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:

Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000), Very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Uncommon: thrombocytopenia
Rare: eosinophilia, leukopenia
Very rare: haemolytic anaemia, aplastic anaemia, agranulocytosis

Immune system disorders
Uncommon: pruritus, dermal and mucosal reactions (see skin and subcutaneous tissue disorders)
Rare: fever, inflammation of blood vessels (vasculitis), renal inflammation (interstitial nephritis), severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (for treatment see section 4.9)

Endocrine disorders
Glucose tolerance may decrease during treatment with furosemide, and hyperglycaemia may occur. This may lead to a deterioration of the metabolic status in patients with manifest diabetes mellitus. Latent diabetes mellitus may become manifest.

Metabolism and nutrition disorders
Impairment of electrolyte and fluid balance as a consequence of increased electrolyte excretion are commonly observed during therapy with furosemide. Regular monitoring of serum electrolytes (especially potassium, sodium and calcium) is therefore indicated.

Possible development of electrolyte disorders is influenced by underlying disorders (e.g. hepatocirrhosis, heart failure), concomitant medication (see section 4.5) and nutrition.

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.

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.

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

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

Metabolic alkalosis may develop, or existing metabolic alkalosis may be exacerbated, as a result of electrolyte and fluid losses during treatment with furosemide.

Hyperuricaemia occurs commonly during furosemide therapy. This may lead to acute episodes of gout in predisposed patients.

Serum levels of cholesterol and triglycerides may be elevated during furosemide treatment.

Nervous system disorders
Rare: paraesthesia

Hepatic encephalopathy can occur in patients with hepatic insufficiency.

Ear and labyrinth disorders
Rare: On account of the ototoxic effects of furosemide, dysacusis and/or syrigmus (tinnitus aurium) can occur, but this is reversible in the majority of cases. This undesirable effect is particularly

associated with too rapid i.v. injection, predominantly in patients with coexisting renal insufficiency or hypoproteinaemia (e.g. in nephrotic syndrome).

Cardiac disorders
In excessive diuresis, circulatory complaints may occur, particularly in elderly patients and in children. These are predominantly manifested as headache, vertigo, dysopia, xerostomia and thirst, hypotension and orthostatic dysregulation. Dehydration and - as a consequence of hypovolaemia - circulatory collapse and haemoconcentration may occur as a result of excessive diuresis. As a result of haemoconcentration, there may be an increased risk of thromboses, particularly in elderly patients.

Vascular disorders
Rare: vasculitis

Gastrointestinal disorders
Rare: gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea)

Hepato-biliary disorders
Very rare: acute pancreatitis, intrahepatic cholestasis, increase in hepatic transaminases

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

4.9 Overdose
Symptoms of an 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 due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

Emergency measures in case of anaphylactic shock
At the first signs (e.g. cutaneous reactions such as urticaria or flush, restlessness, headache, sudden, excessive perspiration, nausea, cyanosis):
- create a venous access
- in addition to other common emergency measures, head-chest down position, ensure airways are clear, administration of oxygen!
- if necessary, initiate further - possibly also intensive care - measures (among others administration of epinephrine, volume replacement, glucocorticoids).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: high-ceiling diuretics
ATC Code: C03CA01

Furosemide is a potent, short and rapid-acting loop diuretic. It inhibits the re-absorption of $Na^+/2Cl^-/K^+$ in the ascending part of Henle's loop by blocking the ion carrier for these ions. The fractional sodium excretion can amount to 35% of the glomerularly filtrated sodium. Increased sodium excretion leads secondarily to increased urinary excretion and to increased distal-tubular K^+-secretion attributable to osmotically bound water. The excretion of Ca^{2+} and Mg^{2+} ions is also increased. Besides the losses of the above-mentioned electrolytes, excretion of uric acid may be reduced, and a shift of the acid-base balance towards metabolic alkalosis may occur.

Furosemide interrupts the tubuloglomerular feedback mechanism at the macula densa, so that the saluretic efficacy is not attenuated.

Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system. In case of cardiac insufficiency, furosemide leads to an acute reduction of the cardiac preload through dilatation of the venous capacitance vessels. This early vascular effect seems to be mediated through prostaglandins and requires sufficient renal function with activation of the renin-angiotensin-aldosterone system as well as intact prostaglandin synthesis.

Furosemide has an antihypertensive effect as a consequence of increased excretion of sodium chloride and reduced responsiveness of vascular smooth muscle cells to vasoconstrictive stimuli, and a reduction in blood volume.

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

a) In renal/hepatic impairment
Where liver disease is present, biliary elimination is reduced. Up to 50% renal impairment has little effect on the elimination rate of furosemide Tablets, but less than 20% residual renal function increases the elimination time.

b) The Elderly
The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

c) New-born
A sustained diuretic effect is seen, possibly due to immature tubular function.

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 tumorigenic 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

microcrystalline cellulose
lactose monohydrate
magnesium stearate
maize starch
sodium starch glycollate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

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

Tablet container
This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Polypropylen/Aluminium blisters
Pack sizes 10, 12, 14, 20, 28, 30, 50, 56, 60, 84, 100 and 250 tablets

HDPE -bottles
Pack sizes: 100 and 250 tablets.

Not all packs sizes or pack types may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

SANDOZ GmbH,KUNDL BIOCHEMIESTRASSE 106250 AUSTRIA.

8. MARKETING AUTHORISATION NUMBER

To be allocated after registration.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

To be allocated after registration.

10. DATE OF (PARTIAL) REVISION OF THE TEXT

February 2016