SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 40 mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of Furosemide

Excipient(s):

Each tablet contains 105mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Round, white to off-white tablet embossed ‘F 40’ on one side (‘F’and ‘40’ seperated by scoreline) and ‘’BL’’ on the other side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide is a potent diuretic with rapid action.

Furosemide tablets are indicated for:

1) The treatment of fluid retention associated with heart failure, including left ventricular failure, cirrhosis of the liver and renal disease, including nephrotic syndrome.

2) The treatment of mild to moderate hypertension (alone, or in combination with other antihypertensive agents in the treatment of more severe cases).

4.2 Posology and method of administration

It is recommended that Furosemide tablets are taken on an empty stomach, and with plenty of liquid**.**

Adults: The initial adult dose is 40mg daily, reduced to 20mg daily or 40mg on alternative days. In some patients daily doses of 80mg or higher (given in divided doses) may be required.

Children: Contra-indicated (see section 4.3)

Elderly: Caution is advised as furosemide is eliminated more slowly in elderly patients.Treatment should be started with 20mg and titrated upwards as required (see section 4.4).

Method of Administration:

For oral administration

4.3 Contraindications

- Hypersensitivity to furosemide or to any of the excipients listed in section 6.1.
- Hypersensitivity to amiloride, sulphonamides or sulphonamide derivatives (because of cross-sensitivity between sulphonamides and furosemide).
- Hypovolaemia or dehydration (with or without accompanying hypotension) (see section 4.4)
- Anuria, or renal failure with anuria not responding to furosemide.
- Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma.
- Pre-comatose and comatose states associated with hepatic cirrhosis (see section 4.4)
- Severe hypokalaemia, severe hyponatraemia. (see section 4.4)
- Breast feeding women (see section 4.6)
- Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m2 body surface area (see section 4.4).
- Addison's disease (see section 4.4).
- Children and adolescents under 18 years of age (safety in this age group has not yet been established).
- Digitalis intoxication (see section 4.5).
- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5).
- Porphyria

4.4 Special warnings and precautions for use:

Particularly careful monitoring or dose reduction is required in:

- elderly patients (lower initial dose as particularly susceptible to side-effects - see section 4.2)
- difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase. Stop furosemide before a glucose tolerance test.
- Pregnancy (see section 4.6)
- patients with gout. Serum uric acid levels tend to rise during treatment with Furosemide and an acute attack of gout may occasionally be precipitated.
- patients with hepatorenal syndrome.
- impaired renal function (see section 4.3 and below-monitoring required)
- impaired hepatic function (see section 4.3 and below-monitoring required)
- Adrenal disease (see section 4.3 and below-monitoring required.)
- 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.
- acute hypercalcaemia (dehydration results from vomiting and diuresis - correct before giving furosemide). Treatment of hypercalcaemia with a high dose of furosemide results in fluid and electrolyte depletion - meticulous fluid replacement and correction of electrolyte required.
- Patients who are at risk from a pronounced fall in blood pressure
- Premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).
- Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Conditions requiring correction before furosemide is started (see also section 4.3)

- hypotension
- hypovolemia
- Severe electrolyte disturbances - particularly hypokalaemia, hyponatraemia and acid-base disturbances.

Furosemide is not recommended

- In patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

Avoidance with other medicines (see also section 4.5 for other interactions

- concurrent NSAIDs should be avoided - if not possible diuretic effect of furosemide may be attenuated
- ACE-inhibitors & Angiotensin II receptor antagonists - severe hypotension may occur - dose of furosemide should be reduced/stopped (3 days) before starting or increasing the dose of these

***Laboratory monitoring requirements*:**

- Serum sodium

Particularly in the elderly or in patients liable to electrolyte deficiency

- Serum potassium

The possibility of hypokalaemia should be taken into account, in particular in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an unbalanced diet and those who abuse laxatives. Regular monitoring of the potassium, and if necessary, treatment with a potassium supplement, is recommended in all cases, but is essential at higher doses and in patients with impaired renal function. It is especially important in the event of concomitant treatment with digoxin, as potassium deficiency can trigger or exacerbate the symptoms of digitalis intoxication (see section 4.5). A potassium-rich diet is recommended during long-term use.
Frequent checks of the serum potassium are necessary in patients with impaired renal function and creatinine clearance below 60ml/min per 1.73m2 body surface area as well as in cases where furosemide is taken in combination with certain other drugs which may lead to an increase in potassium levels (see section 4.5 & refer to section 4.8 for details of electrolyte and metabolic abnormalities).

- Renal function

Frequent BUN in first few months of treatment, periodically thereafter. Long-term/high-dose BUN should regularly be measured. Marked diuresis can cause reversible impairment of kidney function in patients with renal dysfunction. Adequate fluid intake is necessary in such patients. Serum creatinine and urea levels tend to rise during treatment.
The outflow of urine should be ensured. In patients with partial obstruction of the outflow of urine (for example, in patients with disorders in the emptying of the bladder, prostatic hyperplasia or narrowing of the urethra), increased urine output can cause or aggravate these conditions. Thus, these patients require careful monitoring, especially during the initial stages of treatment.

- Glucose

Adverse effect on carbohydrate metabolism - exacerbation of existing carbohydrate intolerance or diabetes mellitus. Regular monitoring of blood glucose levels is desirable.

- Other electrolytes

Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesia (as well as hypokalaemia). During long-term therapy (especially at high doses) it is recommended to carefully and regularly check the electrolytes and especially potassium, magnesium, calcium, chloride, bicarbonate, uric acid and fluid balance. Regular testing of creatinine and urea in the blood is also necessary. Carbohydrate metabolism should also be controlled.

Particularly close control is required in patients who are at high risk of developing disturbances in electrolyte balance or even in case of significant additional fluid loss (e.g. due to vomiting, diarrhea or profuse sweating). Hypovolemia or dehydration as well as any significant disturbance of electrolytes and acid-base balance should be restored. This may require transient discontinuation of furosemide.

***Clinical monitoring requirements (see also section 4.8)*:**
Regular monitoring for

- blood dyscrasias. If these occur, stop furosemide immediately
- liver damage
- idiosyncratic reactions

Other alterations in lab values
Serum cholesterol and triglyceride levels may rise during Furosemide treatment but will usually return to normal within six months of starting furosemide.

Concomitant use with risperidone
In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3 Contraindications).

There is a possibility of exacerbation or activation of systemic lupus erythematosus.

Important information regarding the ingredients of this medicine

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

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

General - The dosage of concurrently administered cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

Food

Although to what extent the absorption of furosemide is affected by its intake with food seems to depend on the pharmaceutical form, it is recommended that the orally administered pharmaceutical forms of Furosemide should be taken on an empty stomach.

Not recommended combinations

In isolated cases after intravenous administration of furosemide and within 24 hours of taking chloral hydrate may develop a burning sensation, sweating, restlessness, nausea, an increase in blood pressure and tachycardia may occur. Therefore, the concomitant administration of furosemide with chloral hydrate is not recommended.

Precautions during use

In patients who are given diuretics, severe hypotension and deterioration of renal function may occur, including cases of renal failure, in particular when an ACE inhibitor or angiotensin II receptor antagonist or angiotensin II receptor antagonist is administered for the first time, or an increased dose for the first time. Therefore, consideration should be given to discontinuing the administration of furosemide temporarily or at least reducing the dose for 3 days before starting treatment with an ACE inhibitor or angiotensin II receptor antagonist or increasing its dose.

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

NSAIDS- Concomitant administration with non-steroidal anti-inflammatory drugs may reduce the action of furosemide. In patients with dehydration or hypovolemia non-steroidal anti-inflammatory drugs may cause acute kidney damage (see section 4.4).

Cardiac glycosides- In concurrent treatment with cardiac glycosides, it should be taken into account that if hypokalaemia and/or electrolyte disturbances (including hypomagnesaemia develop during therapy with furosemide cardiotoxicity is increases.

Drugs that prolong Q-T interval- There is an increased risk toxicity 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.

Anti-hypertensive agents- Enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, furosemide should be stopped or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists (see section 4.4)

Antipsychotics- Furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

Risperidone -Caution should be exercised and the risks and benefits of the combination or co-therapy with furosemide or other potent diuretics should be considered prior to the decision to use. See section 4.4 “Special warnings and precautions for use” regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Anti-arrhythmics- (including amiodarone, disopyramide, flecanaide and sotalol) - risk of cardiac toxicity (because of furosemide induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Vasodilators- enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine

Other diuretics - profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides. Contraindicated with potassium sparing diuretics (e.g. Amiloride spironolactone) - increased risk of hyperkalaemia (see section 4.3)

Patients who had an increased risk of radiocontrast kidney disease and were treated with furosemide had a greater rate of deterioration in renal function after receiving radiocontrast material than high-risk patients who were given intravenous hydration only before receiving radiocontrast agents.

Renin inhibitors - aliskiren reduces plasma concentrations of furosemide given orally. Reduced effect of furosemide might be observed in patients treated with both aliskiren and oral furosemide, and it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly. Monitoring of the diuretic effect of furosemide is recommended at initiation and dose adjustment of concomitant aliskiren therapy.

Nitrates - enhanced hypotensive effect

Antidepressants - enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalaemia with reboxetine

Antidiabetics - hypoglycaemic effects antagonised by furosemide

Antihistamines - hypokalaemia with increased risk of cardiac toxicity

Antifungals - increased risk of hypokalaemia and nephrotoxicity with amphotericin

Anxiolytics and hypnotics - enhanced hypotensive effect. Chloral or triclorfos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) - hypokalaemia increases the risk of ventricular arrhythmias

Potassium salts - contraindicated - increased risk of hyperkalaemia (see section 4.3)

Dopaminergics - enhanced hypotensive effect with levodopa.

Immunomodulators **-** enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosporin and tacrolimus. Concomitant administration of Ciclosporin A and furosemide is associated with an increased risk of gout which is secondary to hyperuricemia caused by furosemide and deficiency of renal excretion of urates from ciclosporin.

Muscle relaxants - enhanced hypotensive effect with baclofen or tizanidine. Furosemide competes with the action of curare-type muscle relaxants and enhances the action of succinylcholine.

Oestrogens - diuretic effect antagonised

Progestogens (drosperidone) **-** increased risk of hyperkalaemia

Prostaglandins - enhanced hypotensive effect with alprostadil

Theophylline **-** enhanced pharmacological effect

Anaesthetic agents **-** general anaesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

Alcohol and Barbiturates - The risk of causing orthostatic hypotension increases with administration of alcohol and barbiturates.

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.

Salicylates- *effexts may be potentiated b furosemide.* Patients receiving high doses of salicylates concomitantly with furosemide, may experience salicylate toxicity.

Chelating-agents- 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 reduced its effect.

Antihypertensives- The effects of other antihypertensives can be potentiated by concomitant administration of furosemide. Severe fall in blood pressure have been observed in combination with ACE inhibitors, furosemide therapy should be temporarily discontinued (or at least the dose reduced) for three days before therapy with an ACE inhibitor is initiated or the dose of an ACE inhibitor is increased. There is a risk of a first-dose effect with post-synaptic

alpha blockers e.g. prazosin. Furosemide may interact with ACE inhibitors causing impaired renal function.

Antibiotics- The toxic effects of nephrotoxic antibiotics (e.g. aminoglycosides or cefaloridine, cephalosporins) may be increased by concomitant administration of potent diuretics such as furosemide**.**
Furosemide may potentiate the ototoxicity of aminoglycosides, polymyxins or vancomycin 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. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hypokalaemia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Carbenoxolone –may increase the risk of developing hypokalaemia.

Cytotoxics -There is a risk of ototoxic effects if platinum compounds/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.

Anti-epileptics- Attenuation of the effect of furosemide may occur following concurrent administration of phenytoin. Concomitant administration of carbamazepine may increase the risk of hyponatraemia.

Corticosteroids - diuretic effect anatgonised (sodium retention) and increased risk of hypokalaemia

Glychyrrizin - (contained in liquorice) may and increase the risk of developing hypokalaemia

Sympathomimetics - increased risk of hypokalaemia with high doses of beta2 sympathomimetics. The action of sympathomimetics that increases blood pressure (e.g. adrenaline, noradrenaline) can be reduced.

Laxative abuse - increases the risk of potassium loss

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

Others: Concomitant administration of aminoglutethimide may increase the risk of hyponatraemia.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of furosemide. Furosemide passes the placenta and reaches 100% of the maternal serum concentration in cord blood. In utero urinary production can be stimulated in the foetus. Urolithiasis has been observed after treatment of premature infants with furosemide. Studies in animals have shown reproductive toxicity (see section 5.3).

Furosemide should only be used if the pathological causes of oedema are not directly or indirectly linked to the pregnancy. Treatment of oedema and hypertension caused by pregnancy with diuretics is not advisable in general as the placental perfusion may be lowered. 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.

Breast-feeding
Furosemide/metabolites are excreted in human milk and can inhibit lactation. The effect of furosemide on newborns/infants is unknown. Breast-feeding should be discontinued during treatment with furosemide (see section 4.3).

Fertility
No human data on the effect of furosemide on fertility are available. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Some adverse reactions (e.g. severe drop in blood pressure) may affect patients ability to concentrate and react and therefore pose a risk in situations where these abilities are of particular importance (e.g. operating machinery or a car). This is of particular importance at the beginning of treatment or when shifting to another drug or in combination with alcohol intake.

4.8 Undesirable effects

The frequencies are derived from data from the literature which refer to studies.

In the case where the frequency category for the same side effect was different, the highest frequency category was chosen.

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: > 1/10000, < 1/1000
Very rare: < 1/10000, including isolated reports	
Not known: frequency cannot be estimated from the available data	

Blood and lymphatic system disorders
Common: hemoconcentration
Uncommon: thrombocytopenia
Rare: eosinophilia, leukopenia, bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should therefore be regularly monitored.
Very rare: haemolytic anaemia or aplastic anaemia, agranulocytosis,

Immune system disorders

Rare: severe anaphylactic or anaphylactic reactions (e.g. with shock).
Not known: exacerbation or activation of systemic lupus erythematosus.

Eye disorders
Uncommon: visual disturbance

Metabolism and nutrition disorders
Very Common: electrolyte abnormalities (including symptomatic), dehydration and hypovolaemia, especially in elderly patients, increased blood creatinine and triglyceride levels.
Common: hyponatremia, hypochloraemia, hypokalaemia, increased blood cholesterol levels, increased blood uric acid levels and gout attacks.
Uncommon: decrease in glucose tolerance. Latent diabetes mellitus can become manifest. See. section 4.4 "Special warnings and precautions for use".
Not known: hypocalcaemia, hypomagnesaemia, increased blood urea, metabolic alkalosis, pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

Nervous system disorders
Rare: paraesthesia, hyperosmolar coma
Common: Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3 “Contraindications”). Therefore, regular monitoring of diuresis and electrolytes and correction of any disturbances are required.
Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension), headache.

Ear and labyrinth disorders
Rare: syrigmus (tinnitus aurium) can occur.
Uncommon: Dysacusis (hearing disorder), although usually transient particularly in patients with renal impairment, hypoproteinaemia (e.g. nephrotic syndrome) and/or when furosemide is administered intravenously very quickly. Cases of deafness (sometimes irreversible) have been reported following administration of furosemide orally or intravenously.

Hepato-biliary disorders
Very rare: cholestasis, increase in transaminases

Vascular Disorder
Very common: hypotension including orthostatic hypotension (see section 4.4 "Special warnings and precautions for use").
Rare: vasculitis
Not known: thrombosis

Skin and subcutaneous tissue disorders
Uncommon: itching, hives, rashes, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reactions.
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS), Lichenoid reactions.

Musculoskeletal and connective tissue disorders
Not known: cases of rhabdomyolysis have been commonly reported in the context of severe hypokalaemia (see section 4.3).

Cardiac disorders
Uncommon: Cardiac arrhythmias
Furosemide may cause reduction in blood pressure .These are predominantly manifested as impairment of concentration and reactions, light headedness, sensations of pressure in the head, vertigo, drowsiness, dysopia, xerostomia and thirst, 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 thrombosis, particularly in elderly patients.

General disorders and administration site conditions
Uncommon: Fatigue
Rare: Malaise

Xanthopsia, thrombophlebitis. hyperuricemia, azotemia; Also common, especially in the elderly and summer months, is dehydration.

Gastrointestinal disorders
Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, constipation.
Gastro-intestinal disorders such as nausea, or gastric upset (vomiting or diarrhoea) and constipation may occur but not usually severe enough to necessitate withdrawal of treatment.
Rare: Diarrhoea, vomiting
Very rare: Acute Pancreatitis

Renal and urinary disorders
Common: Increased urine volume
Uncommon*:* serum creatinine and urea levels can be temporarily elevated during treatment with furosemide.
Rare: interstitial nephritis of the urinary tubules, acute renal failure.
Not known:
- increased levels of sodium in urine, increased levels of chloride in urine, urinary retention (in patients with partial urinary outflow obstruction, see section 4.4 "Special warnings and precautions for use").
- Nephrocalcification/nephrolithiasis in premature neonates (see section 4.4 "Special warnings and precautions for use").
- Renal damage (see section 4.5 "Interactions with other medicinal products and other forms of interaction").

Pregnancy, puerperium and perinatal conditions
In premature infants with respiratory distress syndrome, administration of Furosemide Tablets in the initial weeks after birth entails an increased risk of a persistent patent ductus arteriosus.
In premature infants, furosemide can be precipitated as nephrocalcinosis/kidney stones.
Rare complications may include minor psychiatric disturbances.

Congenital and familial/genetic disorders
Not known: Increased risk of ductus arteriosus open if furosemide is administered to premature infants during the first weeks of life.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after the marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

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

4.9 Overdose

Features
Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypotension and cardiac toxicity. The clinical picture in acute or chronic overdose initially depends on the size and consequences of electrolyte and fluid loss, e.g. hypovolemia, dehydration, haemocondenosis, cardiac arrhythmias (including atrioventricular blockade and ventricular fibrillation). The symptoms of these disorders relate to severe hypotension (progressing to shock), acute kidney damage, thrombosis, delirium states, loose paralysis, apathy and confusion. High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Management

- Benefits of gastric decontamination are uncertain. In patients presenting within 1 hour of ingestion, consider activated charcoal
  (50g for adults)
- Observe for a minimum of 4 hours - monitor pulse and blood pressure.
- Treat hypotension and dehydration with appropriate IV fluids
- Monitor urinary output and serum electrolytes (including chloride and bicarbonate). Correct electrolyte imbalances. Monitor 12
- lead ECG in patients with significant electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: - High-ceiling diuretic sulfonamides, loop diuretics;
ATC code: CO3C A01

• Mode of action

Furosemide is a loop diuretic that reversibly binds to the Na/K/2Cl co-transport mechanism of the thick ascending loop of Henle and possibly also in the proximal and convoluted tubules, inhibiting the active reabsorption of these ions.

Furosemide may also be effective in patients who no longer respond to thiazide and related diuretics, as well as in patients with significantly reduced glomerular filtration.

After oral administration, the effect begins after approximately half an hour and lasts for about 4 to 6 hours, or 6 to 8 hours in edema patients. By increasing the dose to a maximum of 120 mg per day, a stronger diuretic effect can be achieved than with the usual therapeutic doses, particularly if the dose is divided throughout the day.

However, the risk of developing pharmacological side effects also increases with higher doses.

5.2 Pharmacokinetic properties

Absorption:

Furosemide is rapidly absorbed from the gastrointestinal tract. The time of reaching the maximum concentration after administration (tmax) of the 40 mg tablets amounts to 1-1.5 hours. Absorption of the drug shows great inter- and intra-individual variability.

In healthy volunteers the bioavailability of furosemide amounts to about 50%-70% for tablets. The bioavailability of the drug in patients is determined by various factors including concomitant diseases and can be reduced to less than 30% (e.g. in nephrotic syndrome).

To what extent the absorption of furosemide is affected by food intake seems to depend on the pharmaceutical form.

Distribution:

The volume of distribution of furosemide is 0.1-0.2 l/kg body weight.

Furosemide binds for more than 95% to plasma proteins and mainly to albumin.

Elimination:

Furosemide is mainly excreted unchanged, through excretion via the proximal tubule. After intravenous administration of furosemide, 60%-70% of the dose is excreted as parent compound. The glucuronide metabolite of furosemide detected in the urine amounts to approximately 10%-20%. The remaining dose is excreted with the faeces, possibly after biliary secretion.

The final half-life of furosemide after intravenous administration is approximately 1-1.5 hours.

Furosemide is excreted in breast milk. Furosemide crosses the placental barrier and is slowly transferred to the fetus. In the fetus or in the newborn it is found in the same concentrations as in the mother.

• Kidney disease

In renal failure, the elimination of furosemide is decreased and the half-life is increased. The final half-life in patients with severe renal failure is up to 24 hours.

In nephrotic syndrome, decreased plasma protein concentrations lead to increased concentrations of non-binding (free) furosemide.

On the other hand, the activity of furosemide decreases in these patients due to binding to intra-tube albumin and decreased tubular excretion.

Furosemide is poorly removed through haemodialysis, peritoneal refining and CAPD.

•Hepatic insufficiency

In hepatic insufficiency, the half-life of furosemide increases by 30% -90% basically due to the greater volume of distribution.

In addition, in this group of patients there is a large variability in all pharmacokinetic parameters.

• Congestive heart failure, severe hypertension, the elderly

Elimination of furosemide is decreased due to impaired renal function in patients with congestive heart failure, severe hypertension or in the elderly.

• Premature and full-fledged gestational newborns

The elimination of furosemide may be decreased dependent on the maturation of the kidneys. The metabolism of the drug is also reduced in case when the glucuronidation capacity of the fetus is reduced. In infants the final half-life is less than 12 hours at the age of more than 33 weeks after conception. In infants aged 2 months and older, the final clearance is the same as that of adults.

5.3 Preclinical safety data

• ***Acute toxicity***

Toxicity studies where furosemide was administered either orally or intravenously in various rodent and dog species found little acute toxicity. Oral furosemide LD50 ranges between 1050 and 4600 mg/kg body weight in mice and rats, while in guinea pigs it is 243 mg/kg body weight. In dogs or oral LD50 is approximately 2000 mg/kg body weight and intravenous LD50 is more than 400 mg/kg body weight.

• ***Chronic toxicity***

In rats and dogs after 6 and 12 months of administration the renal lesions including local fibrosis, calcification were perceived in the groups that had received the maximum dose (10-20 times greater than the therapeutic dose administered to humans).

• ***Ototoxicity***

Furosemide may interfere with the process of transfer to the vascular horseshoe of the inner ear and may cause auditory disorders which are generally reversible.

• ***Mutagenicity***

In vitro tests carried out on mammalian bacteria and cells found both positive and negative effects. Induction, however, of gene and chromosomal mutations was observed only when cytotoxic concentrations were achieved by furosemide.

• ***Carcinogenicity***

Furosemide was administered in an amount of approximately 200 mg/kg body weight (14,000 ppm) per day together with food in female mice and rats for more than 2 years.

There was an increased incidence of adenocarcinoma of the breasts in mice, but not in rats. This dose is significantly greater than the therapeutic dose administered to sick people. Moreover, these tumors morphologically were the same as the tumors that appeared automatically and were detected in 2% - 8% of the animals under control.

However, this frequency of tumors is unlikely to be related to the treatment administered to humans. Indeed there is no evidence of an increased incidence of adenocarcinoma of the breasts in humans after the administration of furosemide. Based on epidemiological studies, the classification of carcinogenesis due to furosemide in humans is not possible.

In one study on carcinogenicity it was administered to furosemide rats at daily doses of 15 and 30 mg/kg body weight. Male rats at the dose of 15 mg/kg but not at the dose of 30 mg/kg showed a marginal increase in abnormal tumours. These findings are considered to have been random.

The carcinogenicity of the bladder caused by nitrosamine in rats gave no evidence to suggest that furosemide is a propulsion factor.

• ***Reproductive toxicity***

Furosemide did not affect the fertility of male and female rats when administered at daily doses of 90 mg/kg body weight as in male and female mice in daily oral doses of 200 mg/kg body weight.

After administration of furosemide to various mammalian species including the mouse, rat, cat, rabbit and dog, no associated embryotoxic or teratogenic activity was observed. Delayed renal maturation – a decrease in the number of

differentiated glomeruli – was described in the offspring of rats treated therapeutically with 75 mg furosemide per kg of body weight on the days of gestation, i.e. from 7th-11th and 14th-18th days.

Furosemide penetrates the placenta and in the umbilical cord achieves 100% serum concentrations in the mother. To date, some malformations in humans that may be associated with exposure to furosemide have not been detected. Nevertheless, there is not enough experience to make an indisputable assessment of the possible harmful effects on the fetus. Urine production in the fetus can be stimulated in the uterus.

Urolithiasis and nephrocalcinosis were observed after administration of furosemide to premature newborns.

No studies were conducted in order to evaluate the action of furosemide in newborns when introduced with breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Sodium starch glycollate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 4 years

HDPE containers: 3 years

6.4 Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package.

Tablet Containers: Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container

Al/ PVC/PVdC blister, pack sizes of 28, 30, 50, 56, 84, 90, 98, 100 tablets.
HDPE tablet containers, pack sizes of 100, 250, 500 and 1000 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement..

7 MARKETING AUTHORISATION HOLDER

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PL 17907/0019

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04/06/2008

10 DATE OF REVISION OF THE TEXT

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