

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Furosemide Bristol 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of Furosemide.

Excipient(s):

Each tablet contains 105 mg 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' separated 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.

Unsupported 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. Concomitant use of furosemide and 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. When administering risperidone, caution should be exercised and the risks and benefits of the combination or cotreatment with furosemide or with other potent diuretics should be considered prior to the decision to use. See section 4.4 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Anti-arrhythmics- (including amiodarone, disopyramide, flecainide 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)

In patients at high risk of developing contrast-induced nephropathy, furosemide administration may further increase the risk of contrast-induced nephropathy.

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.

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 trichlorfos 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 (drospiridone) - 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- effects may be potentiated by 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 antagonised (sodium retention) and increased risk of hypokalaemia

Glycyrrizin - (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 fetoneonatal 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. unwantedly 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 anaphylactoid reactions (e.g. with shock).

Not known: exacerbation or activation of systemic lupus erythematosus.

Endocrine disorders

Glucose tolerance may decrease during treatment with furosemide. In patients with diabetes mellitus this may lead to a deterioration of the metabolic status in patients with manifest diabetes mellitus. Latent diabetes mellitus may become manifest. Insulin requirements of diabetic patients may increase.

Eye disorders

Uncommon: visual disturbance

Metabolism and nutrition disorders

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

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

Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses,

Symptoms of electrolyte imbalance depend on the type of disturbance.

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, confusion, muscle cramps and weakness, inappetence, dizziness, drowsiness vomiting

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, pareses), intestinal (vomiting, constipation, meteorism), renal (polyuria,) and cardiac (impaired paced setting and conduction disorders) symptoms. Severe potassium losses may lead to paralytic ileus or confusion with coma in extreme cases.

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

Magnesium and calcium deficiency, resulting in tetany or cardiac arrhythmia in rare cases

Nephrocalcinosis/Nephrolithiasis has been reported in premature infants

As with other diuretics treatment with furosemide may lead to transitory increase in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur Serum levels of cholesterol (reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol) and triglycerides may be elevated during furosemide treatment. During long-term therapy they will usually return to normal within six months.

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to hemoconcentration with a tendency for thromboses to develop.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur. For example, in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra.

Nervous system disorders

Rare: paraesthesia, hyperosmolar coma

Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)

Ear and labyrinth disorders

Rare: dysacusis (hearing disorder) and/or syringismus (tinnitus aurium) can occur. 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).

Uncommon: deafness (sometimes irreversible)

Hepato-biliary disorders

Very rare: acute pancreatitis, intrahepatic cholestasis, increase in hepatic transaminases may develop
Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).

Vascular Disorder

Very common: hypotension including orthostatic hypotension

Rare: vasculitis

Not known: thrombosis

Skin and subcutaneous tissue disorders

Uncommon: photosensitivity

Rare: Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, fever, hypersensitivity to light, exudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura, and DRESS (Drug rash with eosinophilia and systemic symptoms).

Not known: acute generalised exanthematous pustulosis (AGEP)

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, headache, 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: Fever, Malaise

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: Increase in urine volume

Uncommon: serum creatinine and urea levels can be temporarily elevated during treatment with furosemide.

Rare: interstitial nephritis, acute renal failure.

Increased urine production, urinary incontinence, can be caused or symptoms can be exacerbated in patients with urinary tract obstruction. Acute urine retention, possibly accompanied by complications, can occur for example in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra.

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

Rare: If furosemide is administered to premature newborns in the first weeks of life, the risk of a patent ductus arteriosus is increased

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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, haemoconcentration, 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 (t_{max}) 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 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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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 and 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 requirements.

7 MARKETING AUTHORISATION HOLDER

Brillpharma (Ireland) Limited
Inniscarra
Main Street
Rathcoole
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22749/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2006

Date of last renewal: 4 May 2008

10 DATE OF REVISION OF THE TEXT

January 2025