SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of Furosemide

Excipients with known effect:

Each tablet contains 52.5mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off-white circular tablets, 6 mm (approx) in diameter, marked ‘F 20’ on one side (F & 20 separated by break line) and ‘’BL’’ on the other side.

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 when brisk diuretic response is required. Alone, or in combination with other antihypertensive agents in the treatment of more severe cases.

4.2 Posology and method of administration

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.

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

Children: Contra-indicated (see section 4.3)

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, sulfonamides (e.g. sulfonamide antimicrobials or sulphonylureas) and thiazides in general may experience cross-sensitivity to furosemide;
- Hypovolaemia and dehydration (with or without accompanying hypotension) (see section 4.4);
- Severe hypokalaemia, severe hyponatraemia. (see section 4.4);
- Pre-comatose and comatose states associated with hepatic cirrhosis (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;
- Impaired renal function with a creatinine clearance below 30 ml/min per 1 .73 m^2 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;
- Breast feeding women (see section 4.6).

4.4 Special warnings and precautions for use

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;

Particular caution and/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;
- Diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test);
- Pregnancy (see section 4.6);
- Gout (furosemide may raise uric acid levels/ precipitate gout);
- Patients with hepatorenal syndrome;
- Impaired hepatic function (see section 4.3 and below- monitoring required)
- Impaired renal function (see section 4.3 and below- monitoring required);
- Adrenal disease (see section 4.3 and below-monitoring required.)
- Hypoproteinaemia, e.g. nephritic syndrome (the effect of furosemide may be impaired and its ototoxicity potentiated- cautious dose titration 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); It also increases the frequency of staying open of the arterial duct and complicates neonatal respiratory distress syndrome.
- 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.

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.

  Urine excretion should be ensured. In patients with partial obstruction of urinary excretion (e.g. in patients with bladder emptying disorders, prostatic hypertrophy or urethral stenosis), increased urine excretion may cause or worsen discomfort. Therefore, careful monitoring of patients is required, 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) potassium, magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured. Regular testing of creatinine and urea in the blood is also necessary. Carbohydrate metabolism must also be controlled.

Particularly frequent screening is required in patients who are at high risk of developing electrolyte balance disorders or even in case of significant additional fluid loss (e.g. due to vomiting, diarrhoea or heavy sweating). Hypovolemia or dehydration, as well as any significant electrolyte and acid-base imbalance, should be restored. This may require temporary 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.

Concomitant use with risperidone
In placebo-controlled studies of risperidone in elderly patients with dementia, higher mortality was observed in patients receiving furosemide and risperidone (7.3%, mean age 89 years, range 75-95 years) compared to patients receiving 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 low-dose thiazide diuretics) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent findings have been observed as to the cause of death. However, caution should be exercised and the risks and benefits of this combination or co-therapy with other potent diuretics should be considered before deciding on use. There was no increased incidence of mortality in patients receiving 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.

Certain electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other medicinal products (e.g. ringworm preparations and drugs that cause QT interval prolongation syndrome).

Food

Whether and to what extent the absorption of furosemide is affected by food intake appears to depend on the pharmaceutical form. It is recommended that the oral pharmaceutical forms of Furosemide be taken on an empty stomach.

Not recommended combinations

In isolated cases, burning sensation, sweating, restlessness, nausea, increased blood pressure and tachycardia may occur. Therefore, the concomitant administration of furosemide with chloral hydrate is not recommended.

Precautions for use

Anti-hypertensive - Patients receiving diuretics may experience severe hypotension and worsening of renal function, including cases of renal failure, particularly when an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin II receptor antagonist or an increased dose is first administered. It is appropriate to consider temporarily discontinuing furosemide administration or reducing the dose for at least 3 days prior to initiation of treatment with an ACE inhibitor or angiotensin II receptor or increasing their 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.

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 co-treatment 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, flecanaide and sotalol) - risk of cardiac toxicity (because of furosemide-induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Cardiac glycosides - Hypokalaemia and electrolyte disturbances (including hypomagnesia) increase the risk of cardiac toxicity.

Drugs that prolong Q-T interval- increased risk of toxicity with furosemide-induced electrolyte disturbances.

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. Monitoring of the diuretic effect of furosemide is recommended at initiation and dose adjustment of concomitant aliskiren therapy.

Nitrates - Enhanced hypotensive effect

Lithium - In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity, including increased risk of cardiotoxic and

neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Chelating-agents - Oral furosemide and sucralfate should not be administered within 2 hours of taking the two substances because sucralfate reduces the absorption of furosemide from the intestine and thus weakens its action. *NSAIDS* - Concomitant administration with non-steroidal anti-inflammatory drugs, including acetylsalicylic acid effects of furosemide. In patients with dehydration or hypovolemia non-steroidal anti-inflammatory drugs may cause acute kidney damage (see section 4.4).

Salicylates - effects may be potentiated by furosemide. Salycylic toxicity may be increased by furosemide.

Antibiotics - Increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. 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.

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.

Anti-epileptics - Increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

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.

Corticosteroids - Diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia

Glycyrrhizin (contained in liquorice) - May and increase the risk of developing hypokalaemia.

Corticosteroids, carbenoxolone, lilyrise in large quantities as well as prolonged use of laxatives may increase the risk of hypokalaemia.

Cytotoxics - Increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. 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.

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, secondary to furosporide- induced hyperuricemia, as well as dysfunction in renal uric acid excretion due to 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

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

Theophylline - Enhanced pharmacological effect

Probenecid and Methotrexate - Effects of furosemide may be reduced by probenecid, methotrexate and furosemide may reduce renal clearance of

probenecid. In contrast, furosemide may reduce the excretion of these drugs by the kidneys. In case of treatment with high doses (particularly when furosemide is co-administered with the other medicinal products), increased serum levels and an increased risk of side effects due to furosemide or due to concomitant treatment may occur.

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.

Laxative abuse - Increases the risk of potassium loss.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is clinical evidence of safety of the drug in the third trimester of human pregnancy &furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxaemia of pregnancy without causing fetal or newborn adverse effects.

However, furosemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons. It should only be used for the pathological causes of oedema which are not directly or indirectly linked to the pregnancy. The treatment with diuretics of oedema and hypertension caused by pregnancy is undesirable because placental perfusion can be reduced, so, if used, monitoring of fetal growth is required.

Breast-feeding

Furosemide is contraindicated as it passes into breast milk and may inhibit lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Some adverse reactions (e.g. a 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 especially important at the beginning of treatment or when changing the medicine or in combination with alcohol intake.

4.8 Undesirable effects

The frequencies are derived from literature data from studies where furosemide was used in a total of 1,387 patients, at any dose and indication.
In the case where the frequency category for the same adverse reaction was different, the higher frequency category was selected.

Undesirable effects can occur with the following frequencies: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1,000, < 1/100), Rare (≥ 1/10,000, < 1,000) and Very rare (< 1/10,000, including isolated reports) and Not Known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Common: hemoconstriction

Uncommon: thrombocytopenia

Rare: leukopenia, eosinophilia

Very rare: agranulocythaemia, aplastic anaemia or haemolytic anaemia

Immune system disorders
Rare: severe anaphylactic or anaphylactic reactions (e.g. with shock).
*Not kno*wn: exacerbation or activation of systemic lupus erythematosus.

Nervous system disorders
Rare: paraesthesia

Common: Hepatic encephalopathy in patients with hepatocellular insufficiency (see section 4.3 "Contraindications"). For this reason, regular monitoring of diuresis and electrolytes and appropriate correction of any disorders is necessary.

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

Eye disorders
Uncommon: Visual disturbance

Ear and labyrinth disorders
Uncommon: Dysacusis (hearing disorder), although usually transient, particularly in patients with renal impairment, hypoproteinaemia (e.g. in nephrotic syndrome) and/or when intravenous administration of furosemide occurs very rapidly. Cases of deafness, sometimes irreversible, have been reported following oral or intravenous administration of furosemide.

Rare: tinnitus of the ears

Cardiac disorders
Uncommon: Cardiac arrhythmias.

Very rare:
Furosemide may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.

Hepato-biliary disorders
Very Rare: In isolated cases, intrahepatic cholestasis, an increase in liver transaminases

Vascular Disorder
*Very comm*on: hypotension including orthostatic hypotension (see section 4.4 "Special warnings and precautions for use")
Rare: Vasculitis
*Not kno*wn: thrombosis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, urticaria, rashes, bumpy dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reaction.

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

Metabolism and nutrition disorders
Very common: electrolyte disturbances (including symptomatic), dehydration and hypogamaemia, especially in elderly patients, increased levels of creatinine and triglycerides in the blood.

Common: hyponatraemia, 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 levels, metabolic alkalosis, Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

General disorders and administration site conditions
Uncommon: Fatigue

Rare: Fever

Xanthopsia, thrombophlebitis. hyperuricemia, azotemia; Dehydration is also common, especially in the elderly and during the summer months.

Gastrointestinal disorders
Uncommon: Dry mouth, thirst, nausea, bowel motility disturbances and constipation. Gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea), malaise 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
Unc*ommon:* 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 Accord 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.

Musculoskeletal and connective tissue disorders

Not known: cases of rhabdomyolysis have been reported commonly in severe hypokalaemia (see section 4.3)

Congenital and family/genetic disorders

Not known: Increased risk of remaining open in the arterial duct if furosemide is administered to premature newborns 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

Symptoms
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 depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias (including atrioventricular blockade and ventricular fibrillation). Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid 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 (50 g for adults; 1 g/kg for children). 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 12lead ECG in patients with significant electrolyte disturbances.

- No specific antidote for furosemide is known. In the case that the intake was made only recently, an effort is required to minimize the further systematic absorption of the active ingredient by taking measures, such as gastric lavage or those recommended to reduce absorption (e.g. activated charcoal).
- Clinically significant fluid and electrolyte balance disorders should be repaired. In addition to the prevention and therapeutic treatment of serious complications arising from such disorders and other effects on the body, it is possible that this corrective action will require special intensive medical monitoring and therapeutic measures to be taken.

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: - High-ceiling diuretic sulfonamides, loop diuretics;
ATC code: C03C A01
Mechanism of action
Furosemide {chemical name: 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid; 4-chloro-N-furfuryl-5-sulfamoyl-anthranilic acid} is a bracket diuretic that creates a comparatively strong and short-term diuresis with rapid onset. Furosemide interferes with the co-transport system of Na+ K+ 2Cl - which is present in the cell membrane of the lumen in the broad anion leg of the Henle bracket: therefore the efficacy of the salt-diuretic action of furosemide depends on the concentration of the substance reaching the tubular lumen through the organic acid pump. The diuretic effect is achieved by inhibiting the reabsorption of sodium chloride in this part of the bracket of Henle. As a consequence of this, fractional sodium elimination can reach 35% of sodium glomerular filtration. Secondary effects of increased sodium excretion are increased urine excretion (due to osmotically bound water) and increased potassium excretion from the cumulative tubule.

The elimination of calcium and magnesium ions is also increased.

Furosemide disrupts the mechanism of retrograde co-regulation of the coil in the proximal threaded tube, resulting in no attenuation of saline diuretic activity. Furosemide causes dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In heart failure, furosemide causes an immediate decrease in the preload of the heart through dilation of the veins. This early vascular activity appears to be related to prostaglandins and presupposes adequate renal function with activation of the renin-angiotensin system and does not affect prostaglandin synthesis. In addition, furosemide, due to its natriuretic action, reduces the

vascular reactivity to catecholamines, which appears to be increased in hypertensive patients.

The antihypertensive effect of furosemide is attributed to increased sodium excretion, decreased blood volume and reduced response of vascular smooth muscle fibers to vasoconstrictive stimuli.

Pharmacodynamic effects
Onset of diuresis following intravenous administration of furosemide occurs within 15 minutes and occurs within 1 hour after oral administration.

In healthy subjects receiving furosemide at doses of 10-100 mg, a dose-dependent increase in diuresis and sodium was observed. The duration of action is approximately 3 hours after intravenous administration of 20 mg furosemide, while after oral administration of 40 mg in healthy subjects it is 3-6 hours.
In patients, the relationship of intratubular concentrations of unbound (free) furosemide (determined by urinary excretion rate) to its natriuretic effect is in the form of an S-curve with a minimum effective excretion rate of furosemide of approximately 10 μg per minute. Therefore, continuous furosemide injection is more effective than repeated bolus injections.
In addition, beyond the specific bolus dose of the drug, there is no significant increase in the effect. The action of furosemide is reduced if tubular excretion or intratubular binding of the drug to albumin is reduced.

5.2 Pharmacokinetic properties

Absorption
Furosemide is rapidly absorbed from the gastrointestinal tract. The time to reach the maximum concentration after administration (tmax) of 40 mg tablets is 1-1.5 hours. The absorption of the drug is highly variable both from person to person and within the same person.

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

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

Distribution
The volume of distribution of furosemide is 0.1-0.2 l/kg body weight. The volume of distribution may be greater than the concomitant disease.

Furosemide is extensively bound to plasma proteins in more than 98% and mainly to albumin.

Elimination

Furosemide is eliminated basically unchanged, initially by excretion from the proximal tubule. Following intravenous administration of furosemide, 60%-70% of the dose is excreted in the same way. The glucuronate metabolite of furosemide, which is detected in the urine, amounts to approximately 10%-20%. The remaining dose is excreted in the faeces, possibly after biliary excretion.

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 foetus. In the foetus or newborn it is found in the same concentrations as in the mother.

• **Kidney disease**

The bioavailability of 500 mg tablets is not differentiated in patients with end-stage renal failure. In renal failure, the elimination of furosemide slows down and the half-life is prolonged. The terminal 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 unbound (free) furosemide.
On the other hand, the activity of furosemide decreases in these patients due to binding to intratubular albumin and impaired tubular excretion.

Furosemide is minimally removed by haemodialysis, peritoneal refining and CAPD.

• ***Liver deficiency***

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

In addition, in this group of patients there is a wide deviation in all pharmacokinetic parameters.

• ***Congestive heart failure, severe hypertension, elderly***

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

• ***Premature and full-term newborns***

The elimination of furosemide may be slowed down depending on kidney maturation. The metabolism of the drug is also reduced in the event that the ability of the foetus to glucogenie is reduced. In infants, the final half-life is less than 12 hours at the age of more than 33 weeks after fertilization. In infants 2 months of age 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 to various rodent species and dogs showed little acute toxicity. The oral LD50 of furosemide 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 about 2000 mg/kg body weight, and the intravenous LD50 is more than 400 mg/kg body weight.

• Chronic toxicity

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

• Ototoxicity

Furosemide may interfere with the transport process in the vascular petal of the inner ear and may cause auditory disturbances which are generally reversible.

• Mutagenic action

In vitro tests conducted on bacteria and mammalian cells found both positive and negative results. Induction of gene and chromosomal mutations was observed only when cytotoxic concentrations from furosemide were achieved.

• Carcinogenic action

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

An increased incidence of breast adenocarcinoma was observed in mice, but not in rats. This dose is significantly higher than the therapeutic dose given to sick people. In addition, these tumors were morphologically identical to the tumors that appeared automatically and were detected in 2% to 8% of the animals under control.

However, this frequency of tumours is considered unlikely to be related to treatment given to humans. Indeed, there is no evidence of an increased incidence of breast adenocarcinoma in humans following furosemide

administration. Based on epidemiological studies, classification of carcinogenicity due to furosemide in humans is not possible.

In one carcinogenicity study, furosemide was administered to rats at daily doses of 15 and 30 mg/kg body weight. Male rats at the 15 mg/kg dose but not at the 30 mg/kg dose showed a marginal increase in unusual tumours. It is believed that these findings were accidental.

Nitrosamine induced bladder carcinogenicity in rats did not provide evidence to suggest that furosemide is a promoter.

• Reproductive toxicity

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

Following administration of furosemide to various mammalian species including mice, rats, cats, rabbits and dogs, no associated foetotoxic or teratogenic effects were observed. Delayed renal maturation – a reduction in the number of differentiated glomerulars – was described in the offspring of rats treated with 75 mg furosemide per kg body weight during gestation days, i.e. from days 7 to 11 and day 14 to 18.

Furosemide crosses the placenta and in the umbilical cord achieves 100% serum concentrations in the mother. To date, no deformities have been detected in humans that may be associated with exposure to furosemide. Nevertheless, there is not enough experience to make an inconclusive assessment of the possible harmful effects on the fetus. The production of urine in the fetus can be stimulated in the uterus.

Urolithiasis and nephrasing have been observed following administration of furosemide to premature newborns.

No studies have been conducted to evaluate the effect 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

Blister packs- 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, 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

Brillpharma Limited,
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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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