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

Excipient(s):

Each tablet contains 52.5mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Round, white to off-white tablet embossed ‘F 20’ on one side 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 (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 any of the excipients of this product.

- 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).
- <u>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</u>.

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 drugswhich 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 isnecessary in such patients. Serum creatinine and urea levels tend to rise during 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 longterm therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

***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).

Important information regarding the ingredients of this medicine

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

4.5 Interaction with other medicinal products and other forms of interaction

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).

NSAIDS- Certain non-steroidal anti-inflammatory agents (e.g.indometacin,ketorolac) may attenuate the action of furosemide (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, flecanaide and sotalol) - risk of cardiac toxicity (because of furosemideinduced 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 (eg Amiloride spironolactone) - increased risk of hyperkalaemia (see section 4.3)

Renin inhibitors - aliskiren reduces plasma concentrations of furosemide

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 ciclosprin and tacrolimus. Increased risk of gouty arthritis with ciclosporin

Muscle relaxants - enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants

Oestrogens - diuretic effect antagonised

Progestogens (drosperidone) - increased risk of hyperkalaemia

Prostaglandins - enhanced hypotensive effect with alprostadil

Theophylline - enhanced hypotensive effect

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

Alcohol - 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. 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 alphablockers eg 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 highdoses 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

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

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 reasons. It should only be used if or the pathological causes of oedema which 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. Treatment during pregnancy requires monitoring of foetal growth is required.

If use of furosemide is essential for the treatment of cardiac or renal insufficiency during pregnancy, careful monitoring of electrolytes, haematocrit and foetal growth is essential. Possible displacement of bilirubin from the albumin binding and thus elevated risk of nuclear icterus in hyperbilirubinaemia is discussed for furosemide.

Furosemide passes the placenta and reaches 100% of the maternal serum concentration in cord blood. No malformations in humans which might be associated with exposure to furosemide have been reported to date. However, there is insufficient experience to allow a concluding evaluation of a potential damaging effect in the embryo/foetus. *In utero* urinary production can be stimulated in the foetus. Urolithiasis has been observed after treatment of premature infants with furosemide.

Lactation

Furosemide passes into breast milk and may inhibit lactation. Women must not breast feed if they are treated with Furosemide (see section 4.3)

4.7 Effects on ability to drive and use machines

Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised that if affected, they should not drive, operate machinery or take part in activities where these effects could put themselves or others at risk.

4.8 Undesirable effects

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

Very common: > 1/10	Common: > 1/100, < 1/10
Uncommon: > 1/1000, < 1/100	Rare: > 1/10000, < 1/1000
Very rare: < 1/10000, including isolated reports	
Not known: frequency cannot be estimated from the available data	

Blood and lymphatic system disorders

Uncommon: thrombocytopenia
Rare: eosinophilia, leukopenia, bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should be therefore be regularly monitored.
Very rare: haemolytic anaemia oraplastic anaemia, agranulocytosis,

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 , results tetania or cardiac arrhythmia in rare cases

Nephrocalcinosis/Nephrolithiasis has been reported in premature infants

Transitor increase in blood creatinine and hyperuricaemia occurs commonly during furosemide therapy. This may lead to acute episodes of gout in predisposed patients.

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 haemoconcentration 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 syrigmus (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
Rare: vasculitis

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, exsudative 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: Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely, fever, Malaise

Gastrointestinal disorders

Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, 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: Acute Pancreatitis

Renal and urinary disorders

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.

Reporting of suspected adverse reactions

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

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 depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion. 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

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation.

Blood-flow is diverted from the juxta-medullary region to the outer cortex.
The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium, chloride from the nephron is reduced hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Approximately 65% of the dose is absorbed after oral administration. The plasma half-life is biphasic with a terminal elimination phase of about 1½ hours. Furosemide is up to 99% bound to plasma proteins and is mainly excreted in the urine, largely unchanged, but also excreted in the bile, non-renal elimination being considerably increased in renal failure. Furosemide crosses the placental barrier and is excreted in the milk.

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

a) In renal/hepatic impairment

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

b) The Elderly

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

c) New-born

A sustained diuretic effect is seen, possibly due to immature tubular function.

5.3 Preclinical safety data

Acute oral toxicity was low in all species tested. Chronic toxicity studies in the rat and dog led to renal alterations (among others fibrous degeneration and renal calcification).

In vitro and *in vivo* tests of genetic toxicology did not reveal any clinically relevant evidence of a genotoxic potential of furosemide.

Long-term studies in mice and rats did not yield any relevant evidence of a tumorigenic potential.

In studies of reproductive toxicology in foetal rats, a reduced number of differentiated glomeruli, skeletal anomalies of the scapulae, humerus and ribs (induced by hypokalaemia), as well as hydronephrosis occurred in foetal mice and rabbits after administration of high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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, 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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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/02/2016