SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide Tablets BP 20mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains furosemide BP 20mg.

Excipient(s) with known effect

Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Uncoated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide Tablets BP 20mg are recommended for use in all indications when a prompt and effective diuresis is required. They are indicated for the maintenance therapy of mild oedema of any origin.

4.2 Posology and method of administration

Posology

Adults:

Initially 40mg in the morning; maintenance 20mg daily or 40mg on alternate days, increasing in resistant oedema to 80mg daily.

Elderly:

Furosemide is generally eliminated more slowly in the elderly. The dosage should be titrated until the required response is achieved.

Paediatric population:

1mg to 3mg/kg daily up to maximum total dose of 40mg/day.

Method of administration: Oral.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Hypersensitivity to amiloride, sulphonamides or sulphonamide derivatives.
- Hypovolaemia or dehydration (with or without accompanying hypotension) (see section 4.4).
- Severe hypokalaemia, severe hyponatraemia (see section 4.4).
- Comatose or pre-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 30ml/min per 1.73m^2 body surface area (see section 4.4).
- Addison's disease (see section 4.4).
- 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.
- Hypovolaemia.
- Severe electrolyte disturbance – particularly hypokalaemia, hyponatraemia and acid-base disturbances.

Furosemide is not recommended

- In patients at high risk for radiocontrast nephropathy – should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.
- In patients with rare hereditary problems of glucose-galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Particular caution and/or dose reduction required:

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

- 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 – contraindication in Addison's disease).
- Hypoproteinaemia e.g. nephrotic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated – cautious dose titration required).
- Acute hypercalaemia (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 (furosemide may cause nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography preformed.

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 and 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 1.73m^2 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.

- 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) 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 triglycerides may rise but usually return to normal within 6 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 cotreatment 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).

This medicine contains less than 1 mmol sodium (23 mg) per 20mg 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).

Antihypertensives – 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 antagonist (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 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) increases 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).

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.

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 – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

NSAIDs – increased risk of nephrotoxicity. Indometacin and ketorolac may antagonise the effects of furosemide (avoid if possible 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 hyponatraemia 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.

Antiepileptics – 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 amphoterecin.

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.

Glychyrrizin – (contained in liquorice) may increase the risk of developing hypokalaemia.

Carbenoxolone – may increase the risk of developing 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.

Anti-metabolites – effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate.

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. 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.

Sympathomimetics – increased risk of hypokalaemia with high doses of $beta_2$ sympathomimetics.

Theophylline – enhanced hypotensive effect.

Probenecid – effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.

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.

Laxative abuse - increases the risk of potassium loss.

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

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

4.7 Effects on ability to drive and operate machinery

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

Undesirable effects can occur with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (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 regularly monitored.

Very rare: Aplastic anaemia or haemolytic anaemia, agranulocytosis

Nervous system disorders:
Rare: Paraesthesia, hyperosmolar coma

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

Endocrine disorders:
Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest. Insulin requirements of diabetic patients may increase.

Eye disorders:
Uncommon: Visual disturbance

Ear and labyrinth disorders:
Uncommon: Deafness (sometimes irreversible)

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

Cardiac disorders:
Uncommon: Cardiac arrhythmias

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.

Hepatobiliary disorders:
In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see section 4.3).

Vascular disorders:
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)

Metabolism and nutrition disorders:
As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride and consequently increase excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased.

Metabolic acidosis can also occur. The risk of this abnormality increases at higher dosages and is influenced by the underlying disorder (e.g. cirrhosis of the liver, heart failure), concomitant medication (see section 4.5) and diet.
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: Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.

Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meterorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances.

Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Nephrocalcinosis/Nephrolithiasis has been reported in premature infants.

Serum cholesterol (reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol) and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

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.

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.

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.

Gastrointestinal disorders such as nausea, 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdosage

Toxicity
The toxicity of diuretics is principally associated with fluid and electrolye loss. More than a few tablets could cause marked effects, particularly in the elderly, however, adults and children who have ingested less than 2 mg/kg are unlikely to

require medical assessment. Peak diuresis and effects on blood pressure are likely to occur within 2 hours of ingestion.

Symptoms
Most patients will not develop serious symptoms but overdose may cause acute, profound diuresis (increased frequency of micturition) resulting in dehydration, volume depletion and electrolyte disturbance. Hypotension, tachycardia, cardiac arrhythmia, hypovolaemia, haemoconcentration hypokalaemia, hypomagnaesemia, hypocalcaemia, hyponatraemia and hypochloraemic alkalosis may occur, with electrolyte depletion causing symptoms such as severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy, weakness, dizziness, confusion, anorexia, lethargy, vomiting, cramps and dysrhythmias.

Dose related adverse effects during therapy have been reported. Myalgia, arthralgia, muscle cramps and weakness occurred in patients receiving doses of between 2 and 10 mg furosemide. High doses have the potential to cause transient deafness and disturbance of uric acid excretion precipitating gout.

Management
- The benefit of gastric decontamination is uncertain, however, activated charcoal (50g for adults; 1 g/Kg for children) should be considered if the patient presents within 1 hour of ingesting a toxic dose.
- Observe for a minimum of 4 hours. Monitor BP and pulse.
- Give i.v. fluids for hypotension and dehydration.
- Monitor urinary output and serum electrolyte levels including chloride and bicarbonate. Correct electrolyte imbalance.
- Perform a 12 lead ECG and measure the QRS duration and QT interval. Repeat 12 lead ECG is recommended, especially in symptomatic patients.
- Other measures as indicated by the patient’s clinical condition.
- Patients should be advised on discharge to seek medical attention if symptoms subsequently develop.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 and a hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis and 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

Furosemide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. It has a biphasic half-life in the plasma with a terminal elimination phase that has been estimated to range up to about 1½ hours. Furosemide is mainly excreted in the urine. Furosemide crosses the placental barrier and is excreted in milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Pregelatinised starch
Talc
Magnesium stearate Microcrystalline cellulose.

6.2 Incompatibilities

Not reported

6.3 Shelf life

36 months for securitainers

36 months for blister packs

6.4 Special precautions for storage

Securitainer: Store in a cool dry place and protect from light

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

6.5 Nature and contents of container

Securitainers and/or tampertainers: Pack sizes: 28, 100, 250, 500 and1,000.

Blister pack (opaque blister strips: 250µm PVC with 60gsm PVDC coating, with 20 µm aluminium foil backing): Pack size 28.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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PL 40147/0038

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