SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg furosemide.

Excipients: Lactose monohydrate 45.0mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White or almost white, circular, flat, bevelled edge tablet with a breakline on one side.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

i) For the management of fluid retention.
ii) For the management of mild to moderate hypertension, either alone or as an adjuvant.

4.2 Posology and method of administration

General:
The dose used must be the lowest that is sufficient to achieve the desired effect. Furosemide has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide is best given as a single dose either daily or on alternative days.

The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved as a maintenance dose. In mild cases, 20 mg daily or 40 mg on alternate days may be sufficient, whereas in cases of resistant oedema, daily doses of 80 mg and above may be used as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. The recommended maximum daily dose of furosemide administration is 1500 mg.

Children:
Oral doses for children range from 1 to 3 mg/kg body weight daily up to a maximum total dose of 40 mg/day.

Elderly:
The dosage recommendations for adults apply, but in the elderly furosemide is eliminated more slowly in general. Dosage should be titrated until the required response is achieved.

4.3 Contraindications

Patients with hypovolaemia or dehydration, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatoxic agents or renal failure

associated with hepatic coma, severe hypokalaemia, severe hyponatraemia, pre-comatose and comatose states associated with hepatic encephalopathy and breast-feeding women.

Hypersensitivity to furosemide or any of the excipients. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use

Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Regular monitoring of serum sodium, potassium and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalance or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute retention and require careful monitoring.

Particularly careful monitoring is necessary in:

- patients with hypotension
- patients at risk from a pronounced fall in blood pressure
- patients with latent or manifest diabetes. Furosemide may necessitate adjustment of control of hypoglycaemic agents in cases of diabetes mellitus
- patients with gout
- patients with hepatorenal syndrome
- 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
- premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

The use of diuretics is considered to be unsafe in acute porphyria therefore caution should be exercised.

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>Concomitant use with risperidone</u>
In risperidone placebo controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or furosemide alone. Caution should be exercised and the risks and benefits of this combination or co-treatment should be considered prior to the decision to use. Dehydration should be avoided.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance and 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

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of the dosage of those drugs.

The harmful effects of nephrotoxic antibiotics on the kidney may be increased.

Impairment of renal function may develop in patients receiving treatment with furosemide and high doses of certain cephalosporins.

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 reduces its effect.

Corticosteroids, corticotrophin and amphotericin B, also cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide.
Corticosteroids administered concurrently may cause sodium retention.

If antihypertensive agents, diuretics or other drugs, with blood-pressure-lowering potential are given concomitantly with furosemide, a more pronounced fall in blood pressure must be anticipated.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Carbenoxolone, liquorice, B_2 sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

Furosemide decreases the excretion of lithium salts and may cause increased serum lithium levels, 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 in patients receiving this combination.

Concomitant use of cyclosporin and furosemide is associated with increased risk of gouty arthritis secondary to furosemide induced hyperurecemia and cyclosporine impairment of renal urate excretion.

Patients who are at high risk of radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.
Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicyclic acid and Indomethacin may reduce the effect of furosemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

Furosemide may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

There is a risk of ototoxic effects if 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.

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).

Attenuation of the effect of furosemide may occur following concurrent administration of phenytoin.

Severe diuresis may occur if metolazone is administered concomitantly.

Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

The effects of antidiabetic drugs and blood pressure increasing sympathomimetics (e.g. epinephrine, norepinephrine) may be reduced. The effects of curare-type muscle relaxants or of theophylline may be increased.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide should be considered prior to the decision to use.

4.6 Fertility, pregnancy and lactation

Furosemide crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Furosemide passes into breast milk and may inhibit lactation. Women must not breast feed if they are treated with furosemide.

4.7 Effects on ability to drive and use machines

Reduced mental alertness may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects

Metabolism and nutrition disorders
- Increased excretion of sodium and chloride and consequently water.
- Increased excretion of other electrolytes (in particular potassium, calcium and magnesium)
- Symptomatic electrolyte disturbances and metabolic alkalosis.
- Hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.
- Transitory increases in blood creatinine and urea levels.
- Increase in cholesterol and triglyceride serum levels.
- Increase in uric acid serum levels and attacks of gout.
- Decrease of glucose tolerance.

Vascular Disorders
- Hypotension including orthostatic hypotension.
- Tendency for thromboses.
- Vasculitis.

Renal and urinary disorders
- Acute retention of urine in patients with a partial obstruction of urinary outflow
- Interstitial nephritis.
- Nephrocalcinosis/nephrolithiasis in premature infants.

Gastrointestinal disorders
- Nausea, vomiting, diarrhoea.
- Acute pancreatitis.

Hepatobiliary disorders
- Intrahepatic cholestasis, increase in liver transaminases.

Ear and labyrinth disorders
- Hearing disorders, tinnitus.
- Deafness (sometimes irreversible) (frequency uncommon)

Skin and subcutaneous tissue disorders
- Itching, urticaria, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, exfoliative dermatitis, purpura, photosensitivity.
- Acute generalised exanthematous pustulosis (AGEP) (frequency not known)

Immune system disorders
- Severe anaphylactic or anaphylactoid reactions.

Nervous system disorders
- Paraesthesiae.
- Hepatic encephalopathy in patients with hepatocellular insufficiency.
- Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension) (frequency not known)

Blood and the lymphatic system disorders
- Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
- Eosinophilia.
- Haemoconcentration.

Congenital and familiar/genetic disorders
- Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

General disorders and administration site conditions
- Following intramuscular injection, local reactions such as pain.
- Fever.

4.9 Overdose

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.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-Ceiling Diuretic Sulfonamide
ATC Code: CO3C A 01

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

Henle with a complex effect on the 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) biosysthesis 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 a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60 – 70 %) on oral administration and its effect is largely over within four hours. The optimal absoption 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 four hours after the drug is given. Furosemide is bound to plasma albumin and little biotransaction 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, bilary elimination is reduced. Up to 50 % renal impairment has little effect on the elimination rate of furosemide, 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 in the newborn, possibly due to immature tubular function.

5.3 Preclinical safety data

Furosemide has not shown mutagenic potential in *in-vitro* or animal tests. There is no evidence of carcinogenicity or of teratological effects in different animal species. Studies in animals failed to demonstrate toxic effects which might be of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Pregelatinised maize starch
Magnesium Stearate
Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container in order to protect from light.

6.5 Nature and contents of container

PP containers with LDPE caps. HDPE film may be used as packing material.

Pack sizes: 30, 100, 250, 500, 1000 and 5000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PA0126/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 03 November 2008

10 DATE OF REVISION OF THE TEXT

March 2016