SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide Tablets BP 40mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg Furosemide PhEur.
Also contains lactose, for the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Appearance: White circular flat bevelled edge 6.0mm tablet embossed PV on one face and F/40 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome.
In the treatment of peripheral oedema due to mild to moderate hypertension (alone, or in combination with other antihypertensive agents in the treatment of more severe cases)
Management of oliguria due to acute or chronic renal insufficiency

4.2 Posology and method of administration

Adults and children over 12 years:
The usual initial daily dose is 40 mg. This may require adjustment until the effective dose is achieved. 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.

In patients with chronic renal insufficiency, an initial daily dose of 250 mg is employed. If a satisfactory diuresis is not produced then the dose may be increased in steps of 250 mg at four to six hourly intervals up to a maximum daily dose of 1,500 mg in 24 hours. In exceptional cases up to 2,000 mg in 24 hours may be given.

Children under 12 years: The oral dose for children ranges from 1 - 3 mg/kg body weight daily, up to a maximum total dose of 40 mg per day.

Elderly: The usual adult dose, but caution is advised as furosemide is excreted more slowly in the elderly. Dosage should be titrated until the required response is achieved.

Method of administration: Oral - the tablets should be swallowed with water.

4.3 Contraindications

Furosemide is contraindicated in the following circumstances

- Hypersensitivity to furosemide, any of its excipients, sulphonamides, sulphonamide derivatives/amiloride
- Anuria and impaired renal function (creatinine clearance below 30mL/min per 1.73 m2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic agents
- Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension (see section 4.4)
- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5)
- Pre-coma/coma associated with hepatic cirrhosis or encephalopathy
- Addison's disease
- Digitalis intoxication (see also section 4.5)
- Breast-feeding women (see section 4.6)

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.

Caution is required in patients liable to electrolyte deficiency.

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 imbalances 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. In moderate liver congestion dosage adjustment may be needed.

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

Particularly careful monitoring is necessary in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure.
- Patients with latent or manifest diabetes. Furosemide may necessitate adjustment of control by hypoglycaemic agents in cases of diabetes mellitus.
- Patients with gout.
- Patients with impaired renal function and hepatorenal syndrome (see section 4.3).
- 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).
- Elderly patients.
- Hepatic failure and alcoholic cirrhosis particularly predispose to hypokalaemia and hypomagnesaemia.
- Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medication which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Regular monitoring for:

- blood dyscrasias. If these occur, stop furosemide immediately
- liver damage
- idiosyncratic reaction

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

Laboratory monitoring requirements:

- frequent BUN in first few months of treatment, periodically thereafter
- serum electrolytes with replacement as appropriate

Other alterations in lab values:

- Serum creatinine and urea levels tend to rise during treatment
- Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide
- Furosemide should be discontinued before a glucose tolerance test
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

Pharmacodynamic interactions of furosemide with other drugs:

An enhanced hypotensive effect may be seen when other antihypertensive (alpha-blockers, ACE inhibitors, angiotensin II receptor antagonists, beta-blockers), vasodilators (moxisylyte or hydralazine), nitrates, anxiolytics and hypnotics, certain classes of antidepressants (MAOIs-Mono Amine Oxidase Inhibitors, TCAs-Tricyclic Antidepressants), phenothiazine, general anaesthetic agents, alcohol, levodopa, prostaglandins (alprostadil), immunomodulatore (aldesleukin), antipsychotics and baclofen are given concomitantly with furosemide.

Concurrent use with ACE inhibitors can result in marked falls in blood pressure. Furosemide should be stopped or the dose reduced before starting an ACE-inhibitor. 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.

An increased risk of hypokalaemia may be seen when amphoterichin, carbenoxolone, corticosteroids/ACTH (synthetic corticosteroids such as prednisolone have a less marked effect, corticosteroids/AIDS may also antagonise the diuretic effect and sodium retention), prolonged use of laxatives, liquorice, other diuretics (acetazolamide, thiazides and related diuretics), reboxetine, beta2 sympathomimetics (salbutamol, terbutaline), tacrolimus and theophylline are given concomitantly with furosemide.

Hypokalaemia and other electrolyte disturbances (including hypomagnesaemia) caused by diuretics such as furosemide can increase the risk of toxicity inherent with other drugs or antagonise their actions;

The cardiac toxicity of digoxin, antihistamines, anti-arrhythmics (amiodarone, disopyramide, flecainide and sotalol) and drugs that induce QT prolongation may be increased.

There is an increased risk of ventricular arrhythmias with certain antipsychotics (amisulpride, sertindole), atomoxetine and pimozide (avoid concomitant use). Enhanced hypotensive effect with phenothiazines. The actions of lidocaine and mexiletine are antagonised.

There may be an increased risk of ototoxicity when furosemide is given with cisplatin, aminoglycosides, polymyxins and vancomycin. Co-administration of cisplatin or ciclosporin with furosemide can enhance nephrotoxicity and increase the risk of hypermagnesaemia. Furosemide can decrease vancomycin serum levels after cardiac surgery.

There may be an increased risk of hyponatraemia when furosemide is given with carbamazepine.
Aliskiren reduces furosemide plasma levels.

Furosemide antagonises the hypoglycaemic effect of hypoglycaemics.

There is an increased risk of nephrotoxicity due to NSAIDs when given with diuretics, while certain NSAIDs (especially indometacin and ketorolac) antagonise the diuretic effect of furosemide. NSAIDs may cause acute renal insufficiency.

Phenytoin reduces the diuretic action of furosemide by up to 50% when given concomitantly.

Profound diuresis is possible when metolazone is given with furosemide.

Avoid the use of diuretics in lymecycline treatment.

There may be an increased risk of osteomalacia when diuretics are taken in combination with phenobarbital.

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

Lipid regulating drugs, bile acid sequestrants (eg colestyramine: colestipol) reduce absorption of furosemide. It should be administered 2 to 3 hours apart.

Salicylates effects may be potentiated by furosemide.

Insulin requirements may be increased (see section 4.4).

Oestrogens and progestogens antagonized the diuretic effect.

Laxative abuse increases the risk of potassium loss.

Pharmacokinetic interactions of furosemide with other drugs:

Furosemide decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in lithium toxicity. Therefore, it is recommended that lithium levels be carefully monitored.

Plasma concentrations of diuretics may be increased by antivirals (nelfinavir, ritonavir or saquinavir).

Plasma concentrations of diuretics may be decreased by barbiturates.

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

4.6 Fertility, pregnancy and lactation
The teratogenic and embryotoxic potential of furosemide in humans is unknown. There is little evidence of safety of high-dose furosemide in human pregnancy, although the results of animal work, in general, show no hazardous effects.

Furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxaemia of pregnancy without causing foetal or newborn adverse effects. However, the drug should not be used in pregnant women unless the benefits to the patient outweigh the possible risk to the foetus which includes persistence of patent ductus arteriosus (section 4.8).

As it may inhibit lactation and passes into breast milk, furosemide should be used with caution in nursing mothers.

4.7 Effects on ability to drive and use machines

Reduced mental alertness and rarely dizziness and blurred vision have been reported. Patients so affected should not drive or operate machines.

4.8 Undesirable effects

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); Frequency not known (cannot be estimated from the available data).

Metabolism and nutritional disorders:
Disturbed balance of electrolytes and water balance (see section 4.4)

Very common: dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene), nephrocalcinosis in infants

Common: Hypovolaemia, hypochloraemia

Uncommon: impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia

Very rare: tetany

Frequency not known: aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, hyperglycaemia.

Furosemide leads to increased excretion of sodium and chloride and consequently water. In addition excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. 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.

Warning signs of electrolyte disturbances include increased thirst, headache, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms.

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

**Eye disorders:**

Uncommon: blurred vision, yellow vision, visual disturbance.

**Ear and labyrinth disorders:**

Uncommonly: deafness (sometimes reversible).

Rare: Hearing disorders, reversible or irreversible loss of hearing and tinnitus, although usually transitory, 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: orthostatic intolerance, cardiac arrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants.

**Vascular disorders:**

Very common: decreased 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)

Uncommon: hypotension, hypovolaemia

Rare: vasculitis, thrombosis, shock

**Skin and subcutaneous tissue disorders:**

Rare: rash, pruritus, photosensitivity, toxic epidermal necrolysis.

Frequency not known: Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, allergic reactions such as skin rashes or bullous lesions, erythema multiforme, exfoliate dermatitis, purpura. When these occur treatment should be withdrawn. Acute generalised exanthematous pustulosis (AGEP).

The incidence of allergic reactions such as skin rash, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low but treatment should be withdrawn when these occur.

**Blood and lymphatic system disorders:**
Uncommon: Aplastic anaemia

Rare: bone marrow depression (necessitate withdrawal of treatment), eosinophilia, leucopenia.

Very rare: thrombocytopenia agranulocytosis, haemolytic anaemia.

**Psychiatric disorder:**

Rare: psychiatric disorder NOC

**Nervous system disorders:**

Rarely: paraesthesiae.

Frequency not known: Headache, confusion, dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).

**Congenital, familial and genetic disorders:**

Rare: In premature infants furosemide may precipitate nephrocalcinosis/nephrolithiasis. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

**Gastrointestinal disorders:**

Uncommon: dry mouth, thirst, nausea, vomiting or diarrhoea, constipation, bowel motility disturbances.

Rare: In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis (in long-term diuretic treatment, including furosemide) may develop.

**Hepatobiliary disorders:**

Rare: intrahepatic cholestasis (jaundice), hepatic function abnormal.

**Musculoskeletal and connective tissue disorders:**

Uncommon: muscle cramps, muscle weakness.

**Renal and urinary disorders:**

Uncommon: reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified).

Rare: nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure.

**General disorders and administration site conditions:**

Uncommon: fatigue

Rare: malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock).
Frequency not known: hypovolaemia.

**Investigations:**

Common: creatinine increased, blood urea increased

Rare: Transaminases increased.

Treatment with furosemide may lead to transitory increases in blood creatinine and urea levels and to an increase in cholesterol and triglyceride serum levels. Serum levels of uric acid may increase and attacks of gout may occur.

**Control of glucose:**

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.

**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; website: www.mhra.gov.uk/yellowcard.

4.9 **Overdose**

In cases of overdosage there is a danger of dehydration, electrolyte depletion and hypotension due to excessive diuresis. In cirrhotic patients, overdosage may precipitate hepatic coma. Treatment should be aimed at fluid replacement and correction of electrolyte imbalance. The drug should be discontinued and electrolyte and water replacement instituted immediately; adjustment should be on the basis of careful monitoring. Gastric lavage may be useful if ingestion is recent.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

ATC code: CO3C A01

Furosemide is one of the high ceiling diuretics, a term used to denote a group of diuretics that have a distinctive action on renal tubular function. The peak diuresis is far greater than that observed with other agents. The main site of action is the thick ascending loop of Henle where they inhibit electrolyte re-absorption. It increases renal blood flow without increasing the filtration rate. Such a change in renal haemodynamics reduces fluid and electrolyte re-absorption in the proximal tubule and may augment the initial diuretic response. Furosemide is an inhibitor of carbonic anhydrase but this activity is too weak to contribute to a proximal diuresis except when massive doses are employed.
Furosemide enhances the excretion of both calcium and magnesium to an extent approximately proportional to the increase in sodium excretion. Unlike the thiazides, high ceiling diuretics do not increase calcium re-absorption in the distal tubule. The calcuiric action of these agents is the basis for their use in symptomatic hypercalcaemia.

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. Bioavailability is about 65%. It has a biphasic half-life in plasma with a terminal elimination phase up to about 2 hours but this is prolonged in neonates, and in patients with hepatic and renal insufficiency. It is extensively bound to plasma proteins but is rapidly secreted by the organic acid transport system of the proximal tubule. In this manner it gains access to the tubular fluid and eventually to its site of action more distally. It is mainly excreted in the urine largely unchanged, but also in the form of glucuronide and free amine metabolites. Variable amounts are also excreted in the bile. Furosemide crosses the placental barrier and is excreted in milk. Non renal elimination is considerably increased in renal failure. The clearance of furosemide is not increased by haemodialysis.

5.3. Preclinical safety data

N/A

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>90.0mg</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0mg</td>
</tr>
<tr>
<td>Maize starch</td>
<td>27.0mg</td>
</tr>
<tr>
<td>Colloidal Silica</td>
<td>1.0mg</td>
</tr>
</tbody>
</table>

6.2. Incompatibilities

No major incompatibilities although certain non steroidal anti-inflammatory agents are known to antagonise the action of frusemide.
6.3. **Shelf life**

5 years.

6.4. **Special precautions for storage**

Will be stored in a dry place below 25°C, protected from light.

6.5 **Nature and contents of container**

1. Tablet container and cap (polypropylene container with low density polyethylene cap).
   - Pack sizes: 28, 56, 100, 250, 500 and 1000 tablets.
2. Blister (250 µm white opaque PVC and 20 µm hard temper aluminium foil).
   - Pack sizes: 28 and 56 tablets.

Not all pack sizes may be marketed.

6.6. **Instruction for use and handling**

None

7 **MARKETING AUTHORISATION HOLDER**

Pharmvit Limited
177 Bilton Road, Perivale
Greenford,
Middlesex
UB6 7HQ

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 04556/0003
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 January 1993 / 17 March 2004

10 DATE OF REVISION OF THE TEXT

16/05/2016