SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 50 mg/5 ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Furosemide 50 mg.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution
Clear, cherry flavoured, oral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide oral solution is indicated in all conditions requiring prompt diuresis in patients who are unable to take solid dose forms. Indications, include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

4.2 Posology and method of administration

Furosemide 50mg/5ml has an exceptionally wide therapeutic range, the effect being proportional to the dosage. Furosemide 50mg/5ml is best given as a single dose either daily or on alternate days.

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

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

_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.

### 4.3 Contraindications

Furosemide 50mg/5ml is contraindicated in 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 hepatotoxic 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 of Furosemide 50mg/5ml. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

### 4.4 Special warnings and precautions for use

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.

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

Particularly careful monitoring is necessary in:
- Patients with hypotension.
- Who are at risk from a pronounced fall in blood pressure.
- Where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- With gout.
- With hepatorenal syndrome.
- 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 of nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

Caution should be observed 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.

This product contains liquid maltitol. Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

**Antihypertensives** – enhanced hypotensive effect possible with all types. 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.

**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.

**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.

**Drugs associated with QT prolongation** – cardiac toxicity may be increased by furosemide-induced hypokalaemia and/or hypomagnesaemia

**Cardiac glycosides** – hypokalaemia and electrolyte disturbances (including magnesium) increases the risk of cardiac toxicity

**Vasodilators** – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine

**Renin inhibitors** – aliskiren reduces plasma concentrations of frurosemide

**Nitrates** – enhanced hypotensive effect

**Lithium** - Furosemide reduces lithium excretion with increased plasma lithium concentrations (risk of toxicity). Avoid concomitant administration unless plasma levels are monitored.

**Chelating agents** – 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) – reduced absorption of furosemide – administer 2 to 3 hours apart

**NSAIDs** – increased risk of nephrotoxicity (especially if there is hypovolaemia). Indometacin and ketorolac may antagonise the effects of furosemide
Salicylates – effects may be potentiated by furosemide

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Possible increased risk of hypokalaemia with reboxetine.

Antidiabetics – hypoglycaemic effects antagonised by furosemide

Insulin - requirements may be increased (see section 4.4)

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin. Barbiturates may decrease plasma concentrations of diuretics. Possible increased risk of osteomalacia when diuretics combined with Phenobarbital

Antihistamines – hypokalaemia with increased risk of cardiac toxicity

Antifungals – increased risk of hypokalaemia with amphoterecin

Antivirals – plasma concentrations of diuretics may be increased by nelfinavir, ritonavir or saquinavir

Anxiolytics and hypnotics – enhanced hypotensive effect.

CNS stimulants (drugs used for ADHD - atomoxetine) – hypokalaemia increases the risk of ventricular arrhythmias

Corticosteroids – diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds.

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of nephrotoxicity (and possibly hypomagnesaemia) with ciclosporin. Increased risk of hypokalaemia with tacrolimus.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine (see also Anaesthetic agents below – curare)

Oestrogens and progestogens – diuretic effect antagonised

Prostaglandins – enhanced hypotensive effect with alprostadil
**Sympathomimetics** – increased risk of hypokalaemia with high doses of beta2 sympathomimetics (such as bambuterol, femoterol, salbutamol, salmeterol and terbutaline)

**Theophylline** – enhanced hypotensive effect: increased risk of hypokalaemia

**Probenecid** – reduced renal clearance of furosemide and decreased diuretic 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

**Laxative abuse** - increases the risk of potassium loss

**Liquorice/carbenoxolone** - excess intake may increase the risk of hypokalaemia

**Potassium salts** – increased risk of hyperkalaemia

**Warfarin/clofibrate** - competition with furosemide in binding to serum albumin – possible significance in patients with low albumin levels (eg nephrotic syndrome). Rapid/profound diuresis with dehydration may reduce antithrombotic effect of warfarin

### 4.6 Fertility, pregnancy and lactation

Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, 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 being treated with furosemide.

### 4.7 Effects on ability to drive and use machines

Mental alertness may be reduced and the ability to drive or operate machinery may be impaired.

### 4.8 Undesirable effects

Furosemide 50mg/5ml is generally well tolerated.
Eosinophilia is rare.

Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment.

Rarely, paraesthesiae may occur.

Serum calcium levels may be reduced; in very rare cases tetany has been observed. Nephrocalcinosis / nephrolithiasis has been reported in premature infants.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy, they will usually return to normal within six months.

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.

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.

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.

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

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock, is very low, but when they occur, treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, erythema multiforme, exfoliative dermatitis, purpura.

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 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, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

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.

If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.

Side effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.

As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

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 – CO3C 1 01

Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

5.2 **Pharmacokinetic properties**

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. In plasma, furosemide is extensively bound to proteins mainly albumin. The unbound fraction in plasma averages 2 – 4% at therapeutic concentrations. The volume of distribution ranges between 170 – 270 ml/Kg. The half life of the ß phase ranges from 45 – 60 min.

Regardless of route of administration, 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. 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.

5.3 **Preclinical safety data**

Furosemide is a widely used diuretic which has been available for over thirty years and its safety profile in man is well established.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Ethanol, sodium hydroxide, cherry flavour (containing propylene glycol), liquid maltitol, disodium hydrogen phosphate, citric acid monohydrate and purified water.

6.2 **Incompatibilities**

None known

6.3 **Shelf-life**

18 months

3 months once opened

6.4 **Special precautions for storage**

Do not store above 25°C.

6.5 **Nature and contents of container**

Bottles: Amber (Type III) glass

Closures:

Polypropylene Child Resistant Closures (CRCs) with LDPE liners

Capacity: 150 ml

6.6 **Instructions for use and handling**

Not applicable.

7. **MARKETING AUTHORISATION HOLDER**

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
8. MARKETING AUTHORISATION NUMBER(S)

PL 04917/0074

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/07/2006

10. DATE OF REVISION OF THE TEXT

13/09/2011