Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 8 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 8mg furosemide.

Excipients with known effect:
Each ml of solution contains 276.8mg maltitol liquid and 79.87mg ethanol (E1510).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

Clear, colourless to pale brown coloured solution with cherry flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide 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

The medication should be administered in the morning to avoid nocturnal diuresis.

Adults(more than 18 years of age):
The usual initial daily dose is 40mg. This may be adjusted until an effective dose is achieved.

Elderly
In the elderly, furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

Paediatric population
This product should not be used in children below 18 years of age (see section 4.4).

This product should not be mixed with food or beverages before use.

Method of administration
For oral administration only

The syringe adaptor should be placed in the neck of the bottle and the required dose should be drawn from the container into the graduated oral syringe provided. The open end of the syringe should be placed in the mouth of the patient, and the piston slowly depressed to release the contents.

4.3 Contraindications

Hypovolaemia or dehydration.
Anuria.
Renal failure with anuria not responding to furosemide, or as a result of poisoning by nephrotoxic or hepatotoxic agents, or associated with hepatic coma.

Severe hypokalaemia and severe hyponatraemia.
Pre-comatose and comatose states associated with hepatic encephalopathy.
Breast feeding.
Hypersensitivity to Furosemide, sulphonamides or to any of the excipients listed in section 6.1.
Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use

This product should not be given to children because its ethanol content may affect their CNS.

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

Urinary output must be secured. Patients with partial obstructions of urinary outflow for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute urinary 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 gout
- Patients with hepatorenal syndrome
- Patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated).

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.

Cautious dose titration is required

- Patients that might manifest latent diabetes
- Diabetic patients who might show increased insulin requirements

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

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).

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.

Excipient Warnings
This product contains:

Ethanol (E1510): This medicinal product contains 79.87mg of alcohol (ethanol) in each ml which is equivalent to 7.987 % w/v. The amount in each ml of this medicinal product is equivalent to less than 2ml beer or 1ml wine. The small amount of alcohol in this medicinal product will not have any noticeable effects.

Maltitol liquid: Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

ACE Inhibitors: Enhanced hypotensive effect when given with diuretics. A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors are added to furosemide therapy. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or increasing the dose of an ACE inhibitor.

Alpha-blockers: Enhanced hypotensive effect when diuretics are given with alpha-blockers, also increased risk of first dose hypotension with post-synaptic alpha-blockers such as prazosin.

Analgesics: Diuretics can increase the risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect. Antagonism of diuretic effect (especially with indomethacin and ketorolac). Salicylic toxicity may be increased by furosemide.
Angiotensin –II Receptor Antagonists: Enhanced hypotensive effect when diuretics given with angiotensin-II receptor antagonists.

Anti-arrhythmics: Hypokalaemia caused by loop diuretics increases cardiac toxicity with amiodarone, disopyramide, flecainide, and antagonises the action of lidocaine and mexiletine.

Antibacterials: Avoid the use of diuretics in lymecycline treatment. There is an increased risk of ototoxicity when loop diuretics are given with aminoglycosides, polymyxins or vancomycin. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Antidepressants: Possible increase of hypokalaemia when loop diuretics are given with reboxetine. There is an enhanced hypotensive effect when diuretics are given with MAOIs. There is an increased risk of postural hypotension when diuretics are given with tricyclic antidepressants.

Antiepileptics: There is an increased risk of hyponatraemia when diuretics are given with carbemazepine. The effects of furosemide are antagonised by phenytoin.

Antifungals: There is an increased risk of hypokalaemia when loop diuretics are given with amphotericin.

Antipsychotics: Hypokalaemia caused by diuretics increase the risk of ventricular arrhythmias with amisulpiride or sertindole. An enhanced hypotensive effect may be seen when diuretics are given with phenothiazines. Hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with pimozide (avoid concomitant use).

Antivirals: Plasma concentration of diuretics may be increased by nelfinavir, ritonavir or saquinavir.

Atomoxetine: Hypokalaemia caused by diuretics increases the risk of ventricular arrhythmias with atomoxetine.

Barbiturates: Plasma concentrations of diuretics may be decreased. There may be an increased risk of osteomalacia when diuretics are taken in combination with Phenobarbital.

Beta-blockers: There is an enhanced hypotensive effect when diuretics are given with beta-blockers. Hypokalaemia caused by loop diuretics increases the risk of ventricular arrhythmias with sotalol.

Cardiac glycosides: Hypokalaemia caused by loop diuretics increases cardiac toxicity with cardiac glycosides.

Ciclosporin: there is an increased risk of nephrotoxicity and possibly hypermagnesaemia when diuretics are given with ciclosporin.

Cisplatin: There is a risk of increased 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. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.
Corticosteroids: The diuretic effect of diuretics is antagonized by corticosteroids. There is an increased risk of hypokalaemia when loop diuretics are given with corticosteroids.

Other Diuretics: There is an increased risk of hypokalaemia when loop diuretics are given with acetazolamide. Profound diuresis is possible when metolazone is given with furosemide. There is an increased risk of hypokalaemia when loop diuretics are given with thiazides and related diuretics.

Lithium: Loop diuretics reduce the excretion of lithium, which may lead to increased plasma concentrations and a risk of toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Potassium salts: There is an increased risk of hyperkalaemia when given with potassium salts.

Sucralfate: Furosemide and sucralfate must not be taken within 2 hours of each other as sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Sympathomimetics, Beta$_2$: There is an increased risk of hypokalameia when loop diuretics are given with high doses of beta$_2$ synpathomimetics.

Tacrolimus: There is an increased risk of hypokalaemia when given with tacrolimus.

Theophylline: There is an increased risk of hypokalaemia when loop diuretics are given with theophylline.

Carbenoxolone, prolonged use of laxatives, liquorice: May increase the risk of developing hypokalaemia.

Warfarin and clofibrate: Warfarin and clofibrate compete with furosemide in the binding to serum albumin. This may have clinical significance in patients with low serum albumin levels (e.g. in nephrotic syndrome). Furosemide does not change the pharmacokinetics of warfarin to a significant extent, but a strong diuresis with associated dehydration may weaken the antithrombotic effect of warfarin.

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.

Risperidone: 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
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 fetal growth.

Lactation:
Furosemide passes into breast milk and may inhibit lactation. Breastfeeding must be avoided during treatment with furosemide.

Fertility:
No human data on the effect of furosemide on fertility are available. In rats, there was no effect on mating or fertility with furosemide treatment.

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

The frequencies of adverse events are ranked according to the following:
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)

System Organ Class	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			Thrombocytopenia	Bone marrow depression, (necessitates withdrawal of treatment), leucopenia, eosinophilia	Agranulocytosis, aplastic anaemia, haemolytic anaemia	
Cardiac disorders			Cardiac arrhythmias			
Congenital, familial and genetic disorders						Increased risk of ductus arteriosus botalli if when furosemide is administered to premature infants within the first weeks of life
Ear and labyrinth disorders			Deafness (sometimes irreversible)	Tinnitus, reversible or irreversible loss of hearing (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)		
Eye disorders			Visual disturbance			
Gastrointestinal disorders			Dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation	Acute Pancreatitis		
General disorders and administration site conditions			Fatigue	Malaise, Fever		
Hepato-biliary						In isolated cases,

disorders						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)
Metabolism and nutrition disorders	Electrolyte disturbances (including symptomatic), hypovolaemia and dehydration (especially in older patients), increased triglyceride levels	Hypochloremia, hypokalemia, increased blood cholesterol, increased blood uric acid and episodes of gout, increased urine volume	Variation in glucose tolerance, a latent diabetes mellitus may become manifest (see section 4.4)			Hypocalcemia, hypomagnesemia, metabolic alkalosis, Bartter syndrome (when misuse and/or prolonged furosemide use)
Musculoskeletal and connective tissue disorders			Muscle cramps, muscle weakness			
Nervous system disorders				Paraesthesia, hyperosmolarcoma		Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).
Psychiatric disorders				Psychiatric disorders NOC		
Renal and urinary disorders			Serum creatinine and urea levels can be temporarily elevated during treatment with furosemide	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
Skin and subcutaneous tissue disorders			Photosensitivity	Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticarial, other rashes or bullous lesions, fever, hypersensitivity to light, exudative erythema multiforme (Lyell's		Acute generalised exanthematous pustulosis (AGEP)

				syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura and DRESS (Drug rash with eosinophilia and systemic symptoms)		
Vascular disorders				Vasculitis		Thrombosis
Immune system disorders				Severe anaphylactic or anaphylactoid reactions		

Premature infants
In general, if furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus. Risk of nephrocalcinosis/ nephroliathisis.

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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms
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 – including A-V block and ventricular fibrillation. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment
There are no specific antidotes to furosemide. If the ingestion is recent, attempts to limit further systemic absorption may be performed, through gastric lavage or others measures that may minimize absorption (i.e. activated charcoal).
The clinically relevant fluid and electrolyte balance changes must be corrected. Along with the prevention and treatment of serious complications resulting from such imbalances and other effects in the body, this corrective action may require general and specific intensive medical monitoring and therapeutic measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-Ceiling Diuretic Sulfonamide ATC code: C03CA01

Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henle. The drug eliminates both positive and negative free water production. 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. 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.

When oral doses of Furosemide are given to normal subjects the mean bioavailability of the drug is approximately 52% but the range is wide. In plasma, Furosemide is extensively bound to proteins mainly to albumin. The unbound fraction in plasma averages 2 - 4% at therapeutic concentrations. The volume of distribution ranges between 170 - 270ml/Kg. The half life of the ß phase ranges from 45 - 60 min. The total plasma clearance is about 200ml/min. Renal excretion of unchanged drug and elimination by metabolism plus faecal excretion contribute almost equally to the total plasma clearance. Furosemide is in part cleared by the kidneys in the form of the glucuronide conjugate.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330)
Ethanol (96% v/v) (E1510)
Sodium hydroxide (E524)
Maltitol liquid
Cherry flavour [containing propylene glycol (E1520)]
Disodium phosphate, anhydrous (E339)
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months
Discard 60 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: Ph.Eur Type III Amber glass

Closure: Tamper evident, child resistant, plastic (Polypropylene/Polyethylene) cap with an EPE liner.

Dosing Device: 10ml oral syringe with 0.5ml graduation mark supplied with an LDPE syringe adaptor.

Pack size: 100ml, 150ml and 300ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0
1 WML
1 Windmill Lane
Dublin 2
D02 F206
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22697/011/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd October 2015
Date of last renewal: 3rd September 2020

10 DATE OF REVISION OF THE TEXT

January 2021