Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fruside 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of furosemide

Excipient with known effect:
Excipients: also contains 63.0 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, flat, bevel-edged tablets, engraved with 2B2 on one tablet side and a single breakline on the reverse.
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

Fruside 40 mg Tablets are indicated for the management of fluid retention, oedema of cardiac, hepatic or renal origin, pulmonary oedema and mild or moderate hypertension.

4.2 Posology and method of administration

Method of administration
For oral administration.

Posology
Adults
The recommended initial dosage is one tablet daily, thereafter adjusted to the minimum effective dose which may range from 1/2 tablet (20 mg) on alternate days to 3 tablets (120 mg) daily.

Children
From 1 to 3 mg/kg body weight daily.

Elderly
In the elderly, elimination of Furosemide is generally slower. Therefore, dosage should be titrated until the required response is achieved.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to sulphonamides.
- Hypovolaemia and dehydration (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.
- Renal failure associated with hepatic coma.
- Severe hypokalaemia; severe hyponatraemia (see section 4.4).
- Pre-comatose or comatose states associated with hepatic encephalopathy (see section 4.4).
- 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.
- Dehydration.
- Significant electrolyte and acid-base disturbances.

Furosemide is not recommended

- In patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose – galactose malabsorption.

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. Fruside 40 mg tablets may necessitate adjustment of control by 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.

Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes (see section 4.8).

Regular monitoring requirements (see also section 4.5 and 4.8):

- Serum sodium.
- Potassium.
- Creatinine

Particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss.

Urinary output must be secured. In patients with a partial obstruction of urinary outflow, increased production of urine may provoke or aggravate complaints. These patients require careful monitoring. 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.

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 when compared to patients treated with risperidone alone or furosemide alone. Cautions should be exercised and the risks and benefits of this combination or co-treatment should be considered prior to the decision to use (see section 4.5). Dehydration should be avoided.

The possibility exists of exacerbation or activation of systemic lupus erythematosus hence caution should be taken when administering furosemide to patients with a history of SLE.

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 (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interactions

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

The harmful effects of nephrotoxic drugs 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. Carbenoxolone, liquorice in large amounts, B2 sympathomimetics, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

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 (see section 4.4).

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

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 ciclosporin 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 patents 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 acetylsalicylic 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.

In isolated cases intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia.

Use of furosemide concomitantly with chloral hydrate is, therefore, not recommended.

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 (see section 4.4).

Levothyroxine: High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breastfeeding
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 the ability to drive or operate machinery.

4.8 Undesirable effects

The frequencies are derived from literature data referring to studies where furosemide is used in a total of 1387 patients, at any dose and in any indication. When the frequency category for the same ADR was different, the highest frequency category was selected.

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

System organ class	Adverse drug reaction

Blood and lymphatic system disorders	
Common	Haemoconcentration
Uncommon	Thrombocytopenia
Rare	Leucopenia Eosinophilia
Very rare	Agranulocytosis Aplastic anaemia Haemolytic anaemia
Immune system disorders	
Rare	Severe anaphylactic or anaphylactoid reactions
Not known	Exacerbation or activation of systemic lupus erythematosus.
Metabolism and nutrition disorders	
Very common	Electrolyte disturbances (including symptomatic), dehydration and hypovolaemia, especially in elderly patients Blood creatinine increased Blood triglyceride increased
Common	Hyponatremia Hypochloremia Hypokalaemia Blood cholesterol increased Blood uric acid increased and attacks of gout Urine volume increased
Uncommon	Glucose tolerance impaired
Not known	Hypocalcemia Hypomagnesemia Blood urea increased Metabolic alkalosis Pseudo-Bartter syndrome
Nervous system disorders	
Common	Hepatic encephalopathy in patients with hepatocellular insufficiency (see section 4.3)
Rare	Paraethesiae
Not known	Dizziness, fainting or loss of consciousness (caused by symptomatic hypotension or by other causes) Headache
Ear and labyrinth disorders	
Uncommon	Hearing disorders. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide
Very rare	Tinnitus
Not known	Deafness (sometimes irreversible)
Vascular disorders	
Very common	Hypotension including orthostatic hypotension
Rare	Vasculitis
Not known	Thrombosis
Gastrointestinal disorders	
Uncommon	Nausea
Rare	Vomiting Diarrhoea
Not known	Pancreatitis acute
Hepatobiliary disorders	
Very rare	Cholestasis Transaminases increased
Skin and subcutaneous tissue disorders	
Uncommon	Pruritus Urticaria Rashes Dermatitis bullous Erythema multiforme Pemphigoid

	Dermatitis exfoliative Purpura Photosensitivity reaction
Not known	Stevens-Johnson syndrome Toxic epidermal necrolysis AGEP (acute generalised exanthematous pustulosis) DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)
Musculoskeletal and connective tissue disorders	
Not known	Cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (see section 4.3).
Renal and urinary disorders	
Common	Urine volume increased
Rare	Tubulointerstitial nephritis
Not known	Urine sodium increased, urine chloride increase, urine retention (in patients with a partial obstruction of urinary outflow, see section 4.4) Nephrocalcinosis/nephrolithiasis in premature infants (see section 4.4) Renal failure (see section 4.5).
Congenital, familial and genetic disorders	
Not known	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	
Rare	Fever
Not known	Following intramuscular injection, local reactions such as pain

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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 of 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 sulphonamides, loop diuretics; ATC code: C03CA01

Mechanism of action

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 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

Absorption
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 4 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.

Biotransformation
Furosemide is bound to plasma albumin and little biotransformation takes place.

Elimination
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.

In renal/ hepatic impairment
Where liver disease is present, biliary elimination is reduced up to 50% Renal impairment has little effect on the elimination rate of Lasix, but less than 20% residual renal function increases the elimination time.

The elderly
The elimination of Furosemide is delayed in the elderly where a certain degree of renal impairment is present.

New born
A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

5.3 Preclinical safety data

Preclinical information has not been included because the safety profile of Furosemide has been established after many years of clinical use. Please refer to section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose (E460)
Sodium starch glycolate (Type A)
Talc (E553b)
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

HDPE or polypropylene containers with caps or child resistant closures in packs of 30, 50, 100, 500, 1000 and 5000 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/087/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 16th August 1993

Date of last renewal: 16th August 2008

10 DATE OF REVISION OF THE TEXT

May 2018