SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

FRUSESCOT (Furosemide Injection USP 20 mg/2ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each ml contains:
Furosemide USP 10mg
Water for Injection USP q.s.

3. PHARMACEUTICAL FORM

Liquid Injection.
Visual/ Physical description of FPP: Clear, colourless solution filled in amber coloured glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Furosemide is a potent diuretic and is recommended for use when prompt and effective diuresis is required.
Furosemide Injection USP 20 mg/2ml are appropriate for use in emergencies or where oral therapy is not feasible. The indications include cardiac, pulmonary, hepatic and renal oedema.

4.2 Posology and Method of Administration

Furosemide Injection USP 20 mg/2ml are for intramuscular or for intravenous administration and must always be given slowly.

Adults: Initially, doses of 20 - 50mg may be administered by the intramuscular route, or by slow intravenous injection at a rate not exceeding 4mg/minute. The diuretic effect of furosemide is proportional to the dosage and, if larger doses are required, they should be given as a controlled infusion at a rate not exceeding 4mg/minute and titrated according to the response.

Elderly: Elimination of furosemide is generally slower in the elderly. Dosage should be titrated until the required effect is achieved.

Paediatric population: Dosages for children range from 0.5 - 1.5mg/kg weight daily up to a maximum total daily dose of 20mg.

Method of administration:
For IV/IM use only.

4.3 Contra-indications

-Hypersensitivity to the active substance or to any of the excipients.
-Hypersensitivity to amiloride, sulphonamides or sulphonamide derivatives
-Hypovolaemia and dehydration (with or without accompanying hypotension)
-Severe hypokalaemia: severe hyponatraemia.
Comatose or pre-comatose states associated with hepatic cirrhosis.
-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

-Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m2 body surface area.
-Addison's disease. Digitalis intoxication.
-Porphyria
-Breast-feeding women.

4.4 Special Warnings and Special Precautions for Use

Conditions requiring correction before furosemide is started
-Hypotension.
-Hypovolaemia.
-Severe electrolyte disturbances – particularly hypokalaemia, hyponatraemia and acid-base disturbances.

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

General- The dosage of concurrently administered cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.
The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.
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).
Antihypertensives – enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, furosemide should be stopped or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists.

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.
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. Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone
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.
Cardiac glycosides – hypokalaemia and electrolyte disturbances (including hypomagnesia) increase the risk of cardiac toxicity.
Drugs that prolong Q-T interval – increased risk of toxicity with furosemide-induced electrolyte disturbances
Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine
Other diuretics – profound diures is possible when furosemide given with metolazone.
Increased risk of hypokalaemia with thiazides.
Renin inhibitors – aliskiren reduces plasma concentrations of furosemide
Nitrates – enhanced hypotensive effect
Lithium - In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, 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 and where necessary the lithium dosage is adjusted in patients receiving this combination.
Chelating agents – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart
NSAIDs – increased risk of nephrotoxicity. Indometacin and ketorolac may antagonise the effects of furosemide. NSAIDs may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.
Salicylates – effects may be potentiated by furosemide. Salycylic toxicity may be increased by furosemide
Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatraemia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.
Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalaemia with reboxetine
Antidiabetics – hypoglycaemic effects antagonised by furosemide
Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antihistamines – hypokalaemia with increased risk of cardiac toxicity
Antifungals – increased risk of hypokalaemia and nephrotoxicity with amphotericin
Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or triclorfos may displace thyroid hormone from binding site.
CNS stimulants (drugs used for ADHD) – hypokalaemia increases the risk of ventricular arrhythmias
Corticosteroids – diuretic effect anatgonised (sodium retention) and increased risk of hypokalaemia
Glychyrrizin -(contained in liquorice) may and increase the risk of developing hypokalaemia.
Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. 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.
Anti-metabolites – effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate
Dopaminergics – enhanced hypotensive effect with levodopa.
Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosprin and tacrolimus. Increased risk of gouty arthritis with ciclosporin
Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants
Oestrogens – diuretic effect antagonised
Progestogens (drosperidone) – increased risk of hyperkalaemia
Prostaglandins – enhanced hypotensive effect with alprostadil
Sympathomimetics – increased risk of hypokalaemia with high doses of beta2 sympathomimetics
Theophylline – enhanced hypotensive effect
Probenecid – effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.
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
Others: Concomitant administration of aminoglutethimide may increase the risk of hyponatraemia.

4.6 Pregnancy and Lactation

Pregnancy

Furosemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons. It should only be used for the pathological causes of oedema which are not directly or indirectly linked to the pregnancy. The treatment with diuretics of oedema and hypertension caused by pregnancy is undesirable because placental perfusion can be reduced, so, if used, monitoring of fetal growth is required. However, furosemide has been given

after the first trimester of pregnancy for oedema, hypertension and toxaemia of pregnancy without causing fetal or newborn adverse effects.

Breast-feeding

Furosemide is contraindicated as it passes into breast milk and may inhibit lactation.

4.7 Effects on Ability to Drive and Use Machines

Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised that if affected, they should not drive, operate machinery or take part in activities where these effects could put themselves or others at risk.

4.8 Undesirable Effects

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, including isolated reports), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Uncommon: thrombocytopenia

Rare: Eosinophilia, Leukopenia, Bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should be therefore be regularly monitored.

Very Rare: aplastic anaemia or haemolytic anaemia, agranulocytosis

Nervous system disorders

Rare: paraesthesia, hyperosmolar coma

Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).

Endocrine disorder

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. Insulin requirements of diabetic patients may increase.

Eye disorders

Uncommon: visual disturbance

Ear and labyrinth disorders

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 intravenons furosemide has been given too rapidly.

Uncommon: Deafness (sometimes irreversible)

Cardiac disorders

Uncommon: Cardiac arrhythmias

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. The diuretic effect of furosemide can result in hypovolaemia and dehydration, especially in the elderly. There is an increased risk of thrombosis.

Hepatobiliary disorders

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop. Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.

Vascular Disorder:

Rare: vasculitis

Skin and subcutaneous tissue disorders

Uncommon: Photosensitivity

Rare: Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, fever, hypersensitivity to light, exsudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).

Not Known: Bullous Pemphigoid

Metabolism and nutrition disorders

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 increase excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased.

Metabolic acidosis can also occur. The risk of this abnormality increases at higher dosages and is influenced by the underlying disorder (e.g. cirrhosis of the liver, heart failure), concomitant medication and diet.

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. Symptoms of electrolyte imbalance depend on the type of disturbance:

Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.

Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meterorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances.

Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Nephrocalcinosis/Nephrolithiasis has been reported in premature infants.

Serum cholesterol (reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol) and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months. As with other diuretics, treatment with furosemide may lead to transitory increase in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur. 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.

Congenital, familial and genetic disorders

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

General disorders and administration site conditions

Uncommon: Fatigue

Rare: Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occurs rarely.,fever, Malaise

Gastrointestinal disorders

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

Rare: Acute Pancreatitis, Gastro-intestinal disorders such as nausea, malaise or gastric upset (vomiting or diarrhoea) and constipation may occur but not usually severe enough to necessitate withdrawal of treatment.

Renal and urinary disorders

Uncommon: serum creatinine and urea levels can be temporarily elevated during treatment with furosemide.

Rare: 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.

Pregnancy, puerperium and perinatal conditions

In premature infants with respiratory distress syndrome, administration of Furosemide in the initial weeks after birth entails an increased risk of a persistent patent ductus arteriosus.

In premature infants, furosemide can be precipitated as nephrocalcinosis/kidney stones.

Rare complications may include minor psychiatric disturbances.

Special population:

-Patients with hepatic impairment

-Pre-existing metabolic alkalosis

4.9 Overdose

Features

Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypotension and cardiac toxicity. High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Management

Benefits of gastric decontamination are uncertain. In patients presenting within 1 hour of ingestion, consider activated charcoal (50g for adults: 1g/kg for children).

Observe for a minimum of 4 hours - monitor pulse and blood pressure.

Treat hypotension and dehydration with appropriate IV fluids.

Monitor urinary output and serum electrolytes (including chloride and bicarbonate). Correct electrolyte imbalances. Monitor 12 lead ECG in patients with significant electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: High-ceiling diuretic sulfonamides, loop diuretics.
ATC Code: C03CA01.

Mechanism of action:
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.

Pharmacodynamic effects:
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 Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.
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:
Approximately 65% of the dose is absorbed after oral administration. The plasma half-life is biphasic with a terminal elimination phase of about 1½ hours.
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.

Distribution:
Furosemide is up to 99% bound to plasma proteins.

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

Elimination:
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%) mainly excreted in the urine, largely unchanged; but also excreted in the bile, non-renal elimination being considerably increased in renal failure. Furosemide crosses the placental barrier and is excreted in the milk.

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

5.3 Preclinical Safety Data
Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Excipient	Grade
1	Sodium Hydroxide	USP
2	Sodium Chloride	USP
3	Water for Injection	USP

6.2 Incompatibilities

Furosemide may precipitate solutions of low pH, and therefore dextrose solutions are not suitable infusion fluids for furosemide injection. The injection solution should not be mixed with other drugs in infusion bottles.

6.3 Shelf Life
24 Months

6.4 Special Precautions for Storage
Store below 30ºC. Protect from light.

6.5 Nature and Contents of Container
10x10x2ml amber glass ampoules packed in a carton along with leaflet.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Scott-Edil Pharmacia Ltd.,
56, EPIP,Phase-I, Jharmajri, Baddi-173205, (HP), INDIA

8. MARKETING AUTHORISATION NUMBER

08662/09771/NMR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 12, 2023

10. DATE OF REVISION OF THE TEXT

Not Applicable.