SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Brand Name: FRUSESKY

Generic Name: FUROSEMIDE INJECTION USP

2. Qualitative and quantitative composition.

Each ml contains:

Furosemide USP ..... 10 mg

Water for Injection USP .....q.s.

3. Pharmaceutical form

Liquid Injection

A clear, colorless solution

4. Clinical particulars

4.1 Therapeutic indications

When a prompt diuresis is required. Use in emergencies or when oral therapy is precluded. Indications include

- Oedema caused by cardiac or hepatic diseases
- Oedema caused by renal diseases (in case of nephrotic syndrome, treatment of the underlying disease is essential)
- Pulmonary oedema (e.g. in case of acute heart failure)

4.2 Posology and method of administration

Route of administration: intravenous or intramuscular

General:

- The parenteral administration of furosemide is indicated in cases where oral administration is not feasible or not efficient (for example in case of reduced intestinal absorption) or when a quick effect is required.
- Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded and should never be given in association with other medicinal products in the same syringe.
- Generally, Furosemide should be administered intravenously. Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration is feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.
- In the absence of conditions requiring a reduced dose (see below) the initial dose recommended for adults and adolescents over 15 years, is of 20 mg to 40 mg

furosemide (1 or 2 ampoules) by intravenous (or in exceptional cases intramuscular) administration; the maximum dose varying according to individual response.

- If larger doses are required, they should be given increasing by 20 mg increments and not given more often than every two hours.
- In adults, the recommended maximum daily dose of furosemide administration is 1500 mg.
- Weight loss induced by enhanced diuresis should not exceed 1 kg/day.

Children and adolescents (up to 18 years of age):

- The intravenous administration of furosemide to children and adolescents below 15 years is only recommended in exceptional cases.
- The dosage will be adapted to the body weight, and the recommended dose ranges from 0.5 to 1 mg/kg body weight daily up to a maximum total daily dose of 20 mg.

Elderly:

- The recommended initial dose is 20 mg/day, increasing gradually until the required response is achieved.

Special dosage recommendations:

For adults, the dose is based on the following conditions:

- Oedema associated to chronic and acute congestive heart failure

The recommended initial dose is 20 to 40 mg daily. This dose can be adapted to the patient´s response, as necessary. The dose should be given in two or three individual doses per day for chronic heart failure and as a bolus for acute congestive heart failure.

- Oedema associated with renal disease

The recommended initial dose is 20 to 40 mg daily. This dose can be adapted to the response as necessary. The total daily dose can be administered as a single dose or as several doses throughout the day.

In patients with nephrotic syndrome the dosage must be determined with caution, because of the risk of a higher incidence of adverse events.

- Oedema associated with hepatic disease

When intravenous treatment is absolutely needed, the initial dose should range from 20 mg to 40 mg. This dose can be adapted to the response as necessary. The total daily dose can be administered as a single dose or in several doses.

Furosemide can be used in combination with aldosterone antagonists in cases in which these agents in monotherapy are not sufficient. In order to avoid complications such as orthostatic intolerance or acid-base and electrolytic

imbalances or hepatic encephalopathy, the dose must be carefully adjusted to achieve a gradual fluid loss. The dose may produce in adults a daily body weight loss of approximately 0.5 kg.

- Pulmonary oedema (in acute heart failure)
  The initial dose to be administered is 40 mg furosemide by intravenous application. If required by the condition of the patient, another injection of 20 to 40 mg furosemide is given after 30 – 60 minutes.
  Furosemide should be used in addition to other therapeutic measures.

4.3 Contraindications

- Hypersensitivity to furosemide or any of the excipients of Furosemide 10 mg / ml Solution for Injection BP.
- Patients with 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
- Patients with severe hypokalaemia or severe hyponatraemia
- Patients with hypovolaemia (with or without hypotension) or dehydration
- Patients in pre-comatose and comatose state associated with hepatic encephalopathy
- Patients with hypersensitivity to sulphonamides (e.g. Sulfonyureas or antibiotics of sulphonamides group) may show cross-sensitivity to furosemide
- Lactation

4.4 Special warnings and precautions for use

Careful monitoring is required in case of:

- Patients with partial obstruction of urinary outflow (e.g. prostatic hypertrophy, hydronephrosis, ureterostenosis). Urinary output must be secured.
- Patients with hypotension or at increased risk from pronounced fall in blood pressure (patients with coronary artery stenosis or cerebral artery stenosis)
- Patients with manifest or latent diabetes mellitus or variation of glycaemia (regular monitoring of blood glucose levels necessary)
- Patients with gout and hyperuricaemia (regular monitoring of uric acid levels in serum necessary)
- Patients with hepatic disease or hepatorenal syndrome (renal impairment associated to severe hepatic disease)
- Hypoproteinaemia (associated to nephrotic syndrome, furosemide´s effect may be reduced and its ototoxicity increased)
- Co-administration with lithium salts (monitoring of lithium levels is required)

- Acute porphyria (the use of diuretics is considered to be unsafe in acute porphyria and caution should be exercised)
- 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.

Cautious dose titration is required:

- Electrolyte variations (e.g. hypokalaemia, hyponatraemia)
- Fluid variations, dehydration, blood volume reduction with circulatory collapse and possibility of thrombosis and embolism, particular in elderly, with excessive use
- Administration of high dosages
- Administration in progressive and severe renal disease
- Administration with sorbitol. Concomitant administration of both substances may lead to increased dehydratation (sorbitol might cause additional fluid loss by inducing diarrhoea)
- Administration in Lupus Erythematosus
- Medication that prolong the QT interval

  Premature infants (possible development of nephrocalcinosis /nephrolithiasis; renal function must be monitored and renal ultrasonography performed). In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life can increase the risk of persistent ductus arteriosus Botalli.

  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. (e.g. due to vomiting or diarrhoea).

  Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

  In patients who are at high risk for radiocontrast nephropathy, furosemide is not recommended to be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

  Photosensitivity: Cases of photosensitivity reactions have been reported. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Athletes:

- The attention of athletes should be drawn to the fact that this drug contains an active ingredient which may give a positive reaction in doping tests.
- This medicinal product contains 0.6mmol sodium per dose of 40mg. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Drug	Interaction	Comments
Alcohol	May aggravate orthostatic hypotension	
Anticonvulsants	Possible reduced diuretic effect	
Antidiabetic agents (e.g., insulin, oral agents)	Possible antagonism of hypoglycemic effect as result of hypokalemia	Observe for possible decreased diabetic control; correct potassium deficit and/or adjust dosage of antidiabetic agent
Antihypertensive agents	Additive antihypertensive effect; orthostatic hypotension may occur	Reduce dosage of both drugs Concomitant therapy generally used to therapeutic advantage
Barbiturates	May aggravate orthostatic hypotension	
Cardiac glycosides (e.g., digoxin)	Possible electrolyte disturbances (e.g., hypokalemia, hypomagnesemia), increased risk of digitalis toxicity, and/or fatal cardiac arrhythmias	Monitor electrolytes; correct hypokalemia
Chloral hydrate	Possible reaction characterized by diaphoresis, flushes, hypertension, and uneasiness in patients with acute MI and heart failure	Consider alternate hypnotic drug (e.g., a benzodiazepine) in patients who require IV furosemide
Diuretics, loop (e.g., bumetanide, ethacrynic acid, torsemide)	Share similar diuretic mechanisms	
Diuretics, potassium-sparing (e.g., amiloride, spironolactone, triamterene)	Possible reduction in potassium loss	May be used to therapeutic advantage
Diuretics, thiazides	Additive diuretic effect	Use reduced dosage of furosemide when added to existing diuretic regimen
Drugs that cause	Additive hypokalemic effects	Monitor electrolytes; correct

potassium loss		hypokalemia
Indomethacin	Possible decreased diuretic and natriuretic effect	Monitor closely to determine if desired diuretic and/or hypotensive effect is obtained
Lithium	Reduced renal clearance of lithium and increased risk of lithium toxicity	Avoid concomitant use; if concomitant therapy is necessary, monitor for lithium toxicity
Neuromuscular blocking agents, nondepolarizing	Potential for prolonged neuromuscular blockade	
Norepinephrine	Decreased arterial responsive to norepinephrine	Norepinephrine may still be used effectively
NSAIAs	Possible weight gain, serum potassium concentrations, and BUN (NSAIAs)	
Ototoxic drugs (e.g., aminoglycoside antibiotics)	Possible additive ototoxic effect, especially in patients with impaired renal function	Avoid concomitant use except in life-threatening situations
Salicylates (e.g., aspirin)	Possible transient reductions in Cl_{cr} in patient with chronic renal insufficiency	Monitor for toxicity
Sucralfate	Possible reduced natriuretic and antihypertensive effects	Do not administer simultaneously; separate administration by ≥2 hours Observe closely for desired diuretic and/or antihypertensive effect
Uricosuric drugs (probenecid, sulfinpyrazone)	Possible antagonism of uricosuric effects	Monitor serum uric acid concentrations

4.6 Fertility, pregnancy and lactation

Use during pregnancy

Furosemide should not be given during pregnancy unless there are compelling medical reasons. Furosemide crosses the placental barrier, and can therefore cause a diuresis of the fetus. Treatment during pregnancy requires monitoring of fetal growth.

Treatment of pregnancy hypertension and oedema is in general not recommended, as physiological hypovolemia can be induced which causes reduction of placental perfusion.

If use of furosemide is essential for the treatment of cardiac or renal insufficiency during pregnancy, careful monitoring of electrolytes, haematocrit and fetal growth is essential. Possible displacement of bilirubin from albumin binding and thus

elevated risk of nuclear icterus in hyperbilirubinaemia is discussed for furosemide. Furosemide can predispose the fetus to hypercalciuria, nephrocalcinosis, and secondary hyperparathyroidism.

Furosemide reaches 100% of the maternal serum concentration in cord blood. No malformations in humans which might be associated with exposure to furosemide have been reported to date. However, there is limited experience to allow a conclusive evaluation of a potential damaging effect in the embryo/fetus.

Use during lactation

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

Patients respond individually to furosemide

The ability to drive or operate machines can incidentally be reduced because of treatment with furosemide, especially at the start of therapy, change of medication or in combination with alcohol.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

As with other diuretics, certain undesirable effects may occur, such as:

Cardiac disorders

In particular, at the initial state of treatment and in elderly, a very intense diuresis may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as orthostatic hypotension, acute hypotension, sensations of pressure in the head, dizziness, circulatory collapse, thrombophlebitis or sudden death (with i.m. or i.v. administration).

Blood and lymphatic system disorders

Uncommon: thrombocytopenia; thrombocytopenia may become manifest, especially with an increase of haemorrhage tendency.

Renal and urinary disorders

Diuretics may exacerbate or reveal acute retention of urine symptoms (bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), vasculitis, glycosuria, transitorily increase of blood creatinine and urea levels.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, dermal and mucosal reactions (e.g. bullous exanthema, rash, urticaria, purpura, exfoliative dermatitis, photosensitivity)

Endocrine disorders

Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of the metabolic control; latent diabetes mellitus may become manifest.

Metabolism and nutrition disorders

Hypokalaemia, hyponatraemia and metabolic alkalosismay occur, especially after prolonged therapy or when high doses are administered. Regular monitoring of serum electrolytes (especially potassium, sodium and calcium) is therefore indicated.

Potassium depletion may occur, especially due to poor potassium diet. Particulary when the supply of potassium is concomitantly reduced and/or extrarenal potassium losses are increased (e.g. in vomiting or chronic diarrhoea) hypokalaemia may occur as a result of increased renal potassium losses.

Underlying disorders (e.g. cirrhotic disease or heart failure), concomitant medication and nutrition may cause predisposition to potassium deficiency. In such cases, adequate monitoring is necessary as well as therapy substitution.

As a result of increased renal sodium losses, hyponatraemia with corresponding symptoms may occur, particularly if the supply of sodium chloride is restricted.

Increased renal calcium losses can lead to hypocalcaemia, which may induce tetania in rare cases.

In patients with increased renal magnesium losses, tetania or cardiac arrhythmias were observed in rare cases as a consequence of hypomagnesaemia.

Uric acid levels may increase and gout attacks may occur.

Metabolic alkalosis may develop, or pre-existing metabolic alkalosis (for e.g. decompensated hepatic cirrhosis) may become more severe with furosemide.

4.1 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 - including AV blockage and ventricular fibrillation) due to excessive diuresis.

Symptoms:

Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment:

At the first signs of shock (hypotension, sudoresis, nausea, cyanosis) the injection should be immediately interrupted, place the patient head down and allow free breathing.

Fluid replacement and correction of the electrolyte imbalance; monitoring of metabolic functions, and maintenance of urinary flux.

Medicinal treatment in case of anaphylactic shock: dilute 1 ml of 1:1000 adrenaline solution in 10 ml and inject slowly 1 ml of the solution (corresponding to 0.1 mg of adrenaline), control pulse and tension and monitor eventual arrhythmias. Adrenaline administration may be repeated, if necessary. Subsequently, inject intravenously a glucocorticoid (for example 250 mg of methylprednisolone), repeating if necessary. Adapt the above-mentioned dosages for children, according body weight.

Correct hypovolaemia with available means and complement with artificial ventilation, oxygen and in case of anaphylactic shock with anti-histamines.

No specific antidote to furosemide is known. If overdose during parenteral treatment has taken place, in principle the treatment consists on follow up and supportive therapy. Haemodialysis does not accelerate furosemide elimination.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics

ATC code: CO3C A01

Furosemide is a strong diuretic agent of fast action. From a pharmacological point of view, furosemide inhibits the co-transport system (reabsorption) of the following electrolytes Na^+, K^+ and $2CL^-$, located on the luminal cell membrane on the ascending limb of the loop of Henle. Consequently, furosemide´s efficiency depends on the drug reaching the tubular lumen through an anionic transport mechanism. The diuretic effect results on the inhibition of sodium chloride reabsorption in this segment of the loop of Henle. As a result, the fraction of excreted sodium may ascend to 35% of sodium glomerular filtration. The secondary effects of increased elimination of sodium are: increase of urinary excretion and increase of potassium distal secretion at the distal tube. Excretion of calcium and magnesium salts is also increased.

Furosemide inhibits the feedback mechanism in the dense macula and induces dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In case of heart failure, furosemide induces an acute reduction of cardiac pre-load (through the enlargement of the blood vessels capacity). This early vascular effect seems to be mediated by prostaglandins and assumes an adequate renal function with activation of the renin-angiotensin system and an intact synthesis of

prostaglandins. Due to its natriuretic effect, furosemide reduces the vascular reactivity to catecholamine that is increased in hypertensive patients.
The diuretic effect of furosemide is established within 15 minutes of an intravenous administration.
A dose-dependent increase in diuresis and natriuresis was found in healthy individuals to whom furosemide was administered (doses between 10 and 100 mg). The duration of action in healthy individuals after the administration of an intravenous 20 mg dose of furosemide is approximately 3 hours.

5.2 Pharmacokinetic properties

Distribution

Furosemide distribution volume is 0.1 to 1.2 litres per kg of body weight. The distribution volume may be increased depending on the concomitant illness.
Protein binding (mostly to albumin) is higher than 98%.

Elimination

Furosemide is mostly eliminated as the non-conjugated form, mainly through secretion at the proximal tube. After intravenous administration, 60% to 70% of furosemide is eliminated by this manner. The glucuronic metabolite of furosemide represents 10% to 20% of the recovered substances in the urine. The remaining dose is eliminated in the faeces, probably after biliary secretion. After intravenous administration, the plasma half-life of furosemide ranges from 1 to 1.5 hours.
Furosemide is excreted in breast milk. It crosses the placental barrier transferring itself slowly to the foetus. Furosemide achieves similar concentrations in the mother, foetus and newborn.

Renal impairment

In case of renal impairment, furosemide´s elimination is slower and its half-life is increased. In patients with end-stage renal disease the average half-life is 9.7 hours. In several multi-organ failure the half life may range from 20-24 hours.
In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unbound furosemide. On the other hand, the efficiency of furosemide is reduced in these patients, due to intratubular albumin binding and to reduced tubular secretion.
Furosemide exhibits low dialysis in patients undergoing haemodialysis, peritoneal dialysis or CAPD (Chronic Ambulatory Peritoneal Dialysis).

Hepatic impairment

In case of hepatic impairment, furosemide´s half-life increases 30% to 90%, mainly due to the higher distribution volume. Biliary elimination might be reduced (up to

50%). In this group of patients, there is a wider variability of the pharmacokinetic parameters.

Congestive heart failure, severe hypertension, elderly
Furosemide elimination is slower due to reduced renal function in patients with congestive heart failure, severe hypertension or in elderly.

Premature infants and new-born
Depending on the maturity of the kidney, elimination of furosemide may be slow. In case of children with insufficient capacity of glucuronidation, the metabolism of the drug is also reduced. In term neonates the half-life is generally less than 12 hours.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on repeated dose toxicity, genotoxicity and carcinogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium Chloride BP
Sodium Hydroxide BP
Hydrochloric Acid BP
Water for Injections USP

6.2 Incompatibilities
Furosemide should not be mixed with strong acid solutions (pH lower than 5.5), such as solutions containing ascorbic acid, noradrenaline and adrenaline, due to the risk of precipitation.

6.3 Shelf life
36 months from the date of manufacturing

6.4 Special precautions for storage
Store at a temperature not exceeding 25ºC, excursion permitted between 15ºC to 30ºC. Protect from light.

6.5 Nature and contents of container
A clear, colorless solution filled in 2 ml amber glass ampoules and 5Nos. of ampoules are packed in a Tray and 5 Nos. of trays packed in a carton with pack insert.

6.6 Special precautions for disposal and other handling

Furosemide 10 mg / ml Solution for Injection may be mixed with neutral and weak alkaline solution with pH between 7 and 10, such as 0.9% sodium chloride and Ringer's lactate solution.

Any unused product or waste material should be disposed of in accordance with local requirements. Product containing visible particles should not be used. For single use only, discard any remaining contents after use.

Furosemide 10 mg / ml Solution for Injection solution should not be mixed with any other drugs in the injection bottle.

7. Marketing authorisation holder

Manufactured By:

Skymap Healthcare Pvt. Ltd
Address: B-2, Dev Bhoomi Industrial Estate,
Puhana Iqbalpur Road, Roorkee-247 667
Distt. Haridwar, Uttarakhand, India

8. Marketing authorisation number(s):

08601/09616/NMR/2022

9. Date of first authorisation/renewal of the authorization:

Apr 18, 2023

10. Date of revision of the text: