1.3 Product information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

1. Name of the Finished Pharmaceutical Product

1.1 Product name:
CODURETICS 'F'
(FUROSEMIDE TABLETS BP 40MG)

1.2 Strength:
Each Uncoated tablet contains:
Furosemide BP 40 mg
Excipients Q.S

1.3 Pharmaceutical dosage forms:
Uncoated Tablet

2. Qualitative and Quantitative composition:

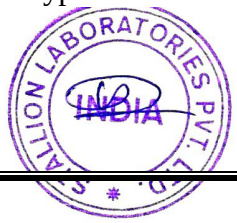
Sr. No.	Ingredients	Label Claim (mg)	Actual Qty/Tablet (mg)	Actual Qty/batch (kg)	Function
Dry Mixing					
1.	Furosemide BP*	40.00	40.000	4.000	Loop diuretic
2.	Maize Starch BP**	----	95.000	9.500	Diluent
3.	Lactose BP	----	68.000	6.800	Diluent
Binding					
5.	Maize Starch BP	----	10.000	1.000	Binder
6.	Sodium Benzoate BP		1.000	0.100	Preservative
7.	Purified Water BP***	----	0.100 ml	10.000 Ltr.	Solvent
Blending & Lubrication					
7.	Sodium Starch Glycolate BP	----	2.500	0.250	Disintegrant
8.	Purified Talc BP	----	5.000	0.500	Lubrication
9.	Magnesium Stearate BP	----	2.500	0.250	Lubrication
10.	Colloidal Anhydrous Silica BP	----	1.000	0.100	Disintegrant
Total Weight of Uncoated Tablet			**225.00 mg**	**22.50 kg**	

*Quantity to be calculated on the basis of its potency.
** Quantity to be compensates on increasing quantity of active material.
*** The materials that will not remain in the final product.

3. Pharmaceutical forms
Tablet

4. Clinical Particulars

4.1 Therapeutic Indications
Furosemide is a diuretic recommended for use in all indications where a prompt and effective diuresis is required.
1) The treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome and pulmonary oedema.
2) The treatment of peripheral oedema due to mechanical obstruction, venous insufficiency, mild to moderate hypertension



4.2 Posology and Method of administration

Posology

Adults and children over 12 years:

Oedema: Initially 40mg daily in the morning; ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced. Diuresis lasts for approximately four hours following administration and hence the time of administration can be adjusted to suit the patient's requirements. Maintenance dose is 20mg daily or 40mg on alternate days, increased in resistant oedema to 80mg daily.

Hypertension: 20-40mg twice daily; if 40mg twice daily does not lead to a clinically satisfactory response, the addition of other antihypertensive agents, rather than an increase in the dose of furosemide should be considered.

Children under 12 years:

A more suitable dosage form should be used in this age group.

Elderly:

Furosemide is generally eliminated more slowly. The dosage should be titrated until the required response is achieved.

Method of Administration

For oral administration

Dosage adjustment may be required

Dosage adjustment may be necessary in patients with

• hypoproteinaemia

• liver congestion/dysfunction

Concomitant administration of the following with furosemide should be considered:

Colestyramine and colestipol - Administer 2 to 3 hours apart

4.3 Contraindications

Furosemide is contraindicated in the following circumstances

• Hypersensitivity to furosemide, any of its excipients, sulphonamides, sulphonamide derivatives/amiloride

• Anuria and impaired renal function (creatinine clearance below 30mL/min per 1.73 m2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic agents

• Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension

• Concomitant potassium supplements or potassium sparing diuretics

• Pre-coma/coma associated with hepatic cirrhosis or encephalopathy

• Addison's disease

• Digitalis intoxication

• Breast-feeding women

4.4 Special warning and precaution 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 glucose-galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Particular caution and/or dose reduction required:

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

• elderly patients (lower initial dose as particularly susceptible to side-effects -

• difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract

• diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test)

• pregnancy

• gout (furosemide may raise uric acid levels/precipitate gout)

• patients with hepatorenal syndrome

• impaired hepatic function

• impaired renal function

• adrenal disease

• hypoproteinaemia e.g. nephrotic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated - cautious dose titration required).

• acute hypercalcaemia (dehydration results from vomiting and diuresis - correct before giving furosemide). Treatment of hypercalcaemia with a high dose of furosemide results in fluid and electrolyte depletion - meticulous fluid replacement and correction of electrolyte required.

• Patients who are at risk from a pronounced fall in blood pressure

• Premature infants (Furosemide may cause nephrocalcinosis/ nephrolithiasis; renal function must be monitored and renal ultrasonography performed)

4.5 Paediatric population

Not applicable

4.6 Interaction with other medicinal products and other forms of interactions

Antihypertensive – 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. Furosemide may interact with ACE inhibitors causing impaired renal function.

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 furosemide.

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. In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal insufficiency.
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.
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 with amphoterecin.
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 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.
Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine (see also *Anaesthetic agents* below – curare).
Oestrogens and progestogens – diuretic effect antagonized.
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.
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 - excess intake may increase the risk of hypokalaemia.

4.7 Additional information on special populations
Not Applicable

4.8 Paediatric population
Not applicable

4.9 Fertility, pregnancy and lactation

Pregnancy

There is clinical evidence of safety of the drug in the third trimester of human pregnancy & furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxaemia of pregnancy without causing fetal or newborn adverse effects. However, 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.

Breast-feeding

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

4.10 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.

4.11 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

Uncommon:

Deafness (sometimes irreversible)

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.
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.
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)..
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.
General disorders and administration site conditions
Uncommon: Fatigue
Rare:
• Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.
• fever
• Malaise
Gastrointestinal disorders
Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation.
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.
Rare:
Acute Pancreatitis
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 Tablets 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.
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 Yellow Card Scheme.

4.12 Overdose and Treatments

Features

Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypotension and cardiac toxicity. 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.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 disturbance.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: High-ceiling diuretic sulfonamides, loop diuretics
ATC code: C03CA01
Mechanism of Action: Furosemide, a loop diuretic, inhibits water reabsorption in the nephron by blocking the sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle. This is achieved through competitive inhibition at the chloride binding site on the cotransporter, thus preventing the transport of sodium from the lumen of the loop of Henle into the basolateral interstitium. Consequently, the lumen becomes more hypertonic while the interstitium becomes less hypertonic, which in turn diminishes the osmotic gradient for water reabsorption throughout the nephron. Because the thick ascending limb is responsible for 25% of sodium reabsorption in the nephron, furosemide is a very potent diuretic.

5.2 Pharmacokinetic Properties

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 up to 99% bound to plasma proteins and is 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.

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

New born

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

5.3 Preclinical Safety data

No further information available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch,
Lactose,
Sodium Benzoate,

Purified water,
Sodium Starch glycolate,
Purified Talc,
Magnesium Stearate,
Colloidal Anhydrous Silica

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
36 months from the date of manufacturing

6.4 Special precautions for storage
Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container
Packing: 10 X 10 Tablets Alu-Alu Blister Pack

Primary Packing: Alu/Alu blister of 10 Tablets packed in Printed Aluminium foil from one side and Plain Aluminium foil from the other side.

Secondary Packing: Such 10 Blisters are packed in printed carton along with package insert.

6.6 Special precautions for disposal and other handling
None

7. Marketing authorisation holder and manufacturing site addresses
STALLION LABORATORIES PVT. LTD.
C-1B 305/2, 3, 4& 5 G.I.D.C. KERALA (BAVLA),
DIST. AHMEDABAD, GUJARAT, INDIA.

8. Marketing authorisation numbers
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9. Date of First Registration/Renewal of the Registration
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10. Date of revision of Text
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11. Dosimetry (If Applicable)
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12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)
