

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Furosemide 40 mg Tablet

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Furosemide

2.2 Quantitative declaration

Each tablet contains 40 mg of Furosemide.

Excipients with known effect:

Each tablet contains Lactose 70 mg

For full list of excipients, see section 6.1

3. Pharmaceutical Form

Uncoated Tablet

Product description

White circular flat bevelled edge tablet embossed C on one side and FM 40 with a breakline on the other side.

‘The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses’

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 ensures, 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 (see section 4.4):

Cholestyramine 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 (see section 4.4)
- Concomitant potassium supplements or potassium-sparing diuretics (see section 4.5)
- Pre-coma/coma associated with hepatic cirrhosis or encephalopathy
- Addison's disease

- Digitalis intoxication (see also section 4.5)
- Breast-feeding women (see section 4.6)

4.4 Special warnings and precautions for use

Hypotension and/or hypovolaemia. (see also section 4.3)

These and any acid-base disturbances should be corrected before furosemide is started. 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.

Dose titration/ adjustment (see section 4.2)

Patients with hypoproteinaemia (such as that associated with the nephrotic syndrome) require careful dose titration (reduced furosemide effect: increased risk of ototoxicity)

In moderate liver congestion dosage adjustment may be needed

Caution required:

Caution needed in the following circumstances

impaired hepatic function (see sections 4.2 & 4.3 and below – monitoring required) impaired renal function and hepato-renal syndrome (see section 4.3 and below – monitoring required) diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase) elderly patients difficulty with micturition/potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention) gout (increased risk of hyperuricaemia) patients at risk of pronounced falls in blood pressure

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for

blood dyscrasias. If these occur, stop furosemide immediately liver damage and idiosyncratic reactions. In premature infants there is a risk of development of nephrocalcinosis/nephrolithiasis. Renal function must be monitored and renal ultrasonography performed.

Laboratory monitoring requirements:

Frequent BUN in first few months of treatment, periodically thereafter serum electrolytes with replacement as appropriate

Other alterations in lab values

Serum creatinine and urea levels tend to rise during treatment

Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide

Furosemide should be discontinued before a glucose tolerance test

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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).

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.

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

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.

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.

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

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

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, Beta₂: There is an increased risk of hypokalaemia when loop diuretics are given with high doses of beta₂ 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.

Aliskiren reduces the plasma concentration of furosemide given orally. Reduced effect of furosemide might be observed in patients treated with both aliskiren and oral furosemide, and it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly.

4.6 Pregnancy and lactation

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.

Breast-feeding

Furosemide passes into breast milk and may inhibit lactation. Women must not

breastfeed if they are treated with furosemide.

Fertility:

No human data on the effect of furosemide on fertility are available.

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 toxemia 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.

Lactation

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 and rarely, dizziness and blurred vision have been reported. Patients so affected should not drive or operate machinery.

4.8 Undesirable Effects

The following classification of CIOMS frequencies according to the MedDRA database is used where applicable: Very common $\geq 1/10$; Common $\geq 1/100$, $<1/10$; Uncommon $\geq 1 / 1,000$, $<1/100$; Rare $\geq 1 / 10,000$, $<1 / 1,000$; Very rare $<1 / 10,000$; Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:	Uncommon:	aplastic anaemia
	Rare:	bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leucopenia.
	Very rare:	haemolytic anaemia, agranulocytosis, thrombocytopenia, vasculitis.
Metabolism and nutritional disorders:	Very common	dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesaemia (incidences of the last three are reduced by triamterene), nephrocalcinosis in infants
	Common:	Hypovolaemia, hypochloraemia
	Uncommon:	impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia
	Very rare:	tetany
	Frequency not known:	aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, hyperglycaemia.
Psychiatric disorder:	Rare:	psychiatric disorder

Nervous system disorders:	Rare:	paraesthesia, confusion, headache, dizziness.
	Not known :	Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension).
Eye disorders:	Uncommon:	visual disturbance, blurred vision, yellow vision.
Ear and labyrinth disorders:	Uncommon:	deafness (sometimes irreversible)
	Rare:	tinnitus and reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome)
Cardiac disorders:	Uncommon:	orthostatic intolerance, cardiac arrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants.
Vascular disorders:	Very common:	decreased 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).
	Uncommon:	hypotension, hypovolaemia
	Rare:	vasculitis, thrombosis, shock
Gastrointestinal disorders:	Uncommon:	dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation
	Rare:	acute pancreatitis (in long-term diuretic treatment, including furosemide).
Hepatobiliary disorders:	Rare:	pure intrahepatic cholestasis (jaundice), hepatic function abnormal.
Skin and subcutaneous tissue disorders:	Rare:	rash, pruritus, photosensitivity, toxic epidermal necrolysis.
	Not known:	urticaria, erythema multiforme, purpura, exfoliative dermatitis, itching, allergic reactions, such as skin rashes, various forms of dermatitis including urticaria, bullous lesions,. When these occur treatment should be withdrawn. Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders:	Uncommon:	muscle cramps, muscle weakness.
Renal and urinary disorders:	Uncommon:	reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified).
	Rare:	nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure.
Congenital, familial and genetic disorders:	Rare:	patent ductus arteriosus
General disorders and administration site conditions:	Uncommon:	Fatigue
	Rare:	malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock).
Investigations:	Common:	creatinine increased, blood urea increased

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 and the general public are advised to report via National Pharmacovigilance Electronic Reporting Systems to the

respective National Regulatory Authorities.

4.9 Overdose

a) Signs and symptoms:

The clinical picture in acute or chronic over dosage depends primarily on the extent and consequences of loss of electrolytes and fluids (e.g. hypovolemia, dehydration, hemoconcentration, cardiac arrhythmia - including A-V block and ventricular fibrillation). Symptoms of these changes include: severe hypotension (and progression to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

b) Treatment:

There is no known specific antidote for furosemide. If ingestion is very Attempts may be made to limit more extensive systemic absorption of active substance, through measures such as gastric lavage or other measures intended to reduce absorption (e.g. use of activated charcoal).

Changes in clinically relevant fluid and electrolyte balance must be corrected. Together with the prevention and treatment of serious complications resulting from such imbalances and other effects on the body, this corrective action may require intensive generalist and specific medical monitoring, as well as of therapeutic measures.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Cardiovascular apparatus. Antihypertensives.
Diuretics, loop diuretics
ATC code: **C03CA01**

Mechanism of action:

Furosemide is a potent, fast-acting diuretic with a rapid onset of action. From the pharmacological point of view, furosemide inhibits co-transport system (reabsorption) of the Na⁺, K⁺ and - Cl² electrolytes, located of the luminal cell membrane of the ascending branch of the Hanley loop consequently, the efficacy of the saluretic action of furosemide depends on the product reaches the tubular lumen through a transport mechanism anionic. Diuretic action results from the inhibition of sodium chloride reabsorption in this segment of the loop of Henle. As a result, the fraction of sodium excreted may to 35% of glomerular sodium filtration. Side effects of excretion increased urinary excretion and increased distal secretion of potassium at the level of the distal tubule. The excretion of calcium and magnesium ions is increased.

Furosemide disrupts the tubulo-glomerular feedback mechanism in the macula dense, resulting in non- attenuation of saluretic activity.

Furosemide causes dose-dependent stimulation of the renin-angiotensin-aldosterone system.

In case of heart failure, furosemide causes an acute reduction in preload (by increasing the capacitance of blood vessels). This vascular effect seems to be mediated by prostaglandins and with the activation of the renin-angiotensin

system and an intact synthesis of prostaglandins.

Apart from the fact that, given its furosemide decreases the vascular reactivity to catecholamines, which is increased in hypertensive patients.

The antihypertensive efficacy of furosemide is attributable to increased excretion of sodium, blood volume reduction and vascular smooth muscle response to the stimulus vasoconstrictor.

5.2 Pharmacokinetic Properties

Furosemide is rapidly absorbed from the gastrointestinal tract. The t_{max} is 1 to 1.5 hours in the case of Furosemide 40 mg. Absorption of the drug denotes a broad intra and interindividual variability.

The bioavailability of furosemide in healthy volunteers is approximately 50% 70% for tablets. In the case of sick individuals, the bioavailability of drug is influenced by several factors, including concomitant diseases, can be reduced by around 30% (for example in the case of nephrotic).

The fact that the absorption of furosemide may be affected by food intake and effect seems to depend on the pharmaceutical formulation in question. The volume of distribution of furosemide is 0.1 to 1.2 liters per kg of body weight.

The plasma protein binding (mostly to albumin) is greater than 98%. Furosemide is mostly eliminated in the non-conjugated form, mainly by secretion at the level of the proximal tubule. Following intravenous administration, 60% to 70% of the furosemide dose is excreted in this way. The glucuronic metabolite of furosemide represents 10% to 20% of the substances recovered in the urine. The remaining dose is excreted in the faeces, probably after biliary secretion.

The terminal half-life of furosemide after intravenous administration is approximately 1 to 1.5 hours. Furosemide is excreted in breast milk.

Furosemide crosses the barrier the placenta slowly transferring to the fetus.

Furosemide reaches concentrations identical in the mother and in the fetus or newborn.

Renal insufficiency

In case of renal insufficiency, the elimination of furosemide is slower and its half-life is prolonged, the terminal half-life may reach 24 hours in patients with severe renal impairment.

In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unconjugated (free) furosemide are achieved. Per On the other hand, the efficacy of furosemide is reduced in these patients, due to the intratubular albumin and decreased tubular secretion.

Furosemide is poorly dialysable in patients receiving hemodialysis, dialysis peritoneal or CAPD (Chronic Ambulatory Peritoneal Dialysis).

Hepatic insufficiency

In case of hepatic impairment, the half-life of furosemide in the order of 30% to 90%, mainly due to the higher volume of high. In addition, in this group of patients there is pharmacokinetic parameters. Congestive heart failure, severe hypertension, elderly Elimination of furosemide is slowed due to reduced renal

function in patients with congestive heart failure, severe hypertension or in the elderly.

Premature and newborn infants

Depending on the maturity of the kidney, elimination of furosemide may be slower. The metabolism of the drug is also reduced in the case of children with insufficiency of glucuronization capacity. The terminal half-life is less than 12 hours in children with a post-conception age greater than 33 weeks. In children with terminal age is equal to that of adults.

5.3 Preclinical safety data

Not applicable.

6 Pharmaceutical Particulars

6.1 List of Excipients

Lactose BP
Maize Starch BP
Potassium Sorbate BP
Sodium Lauryl Sulphate BP
Croscarmellose sodium BP dried
Magnesium Stearate BP

6.2 Incompatibilities

None

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.4 Nature and contents of container

PVC/ALU blister packing
Available in Pack sizes of 2 X 14 tablets, 4 X 14 tablets, 8 X 14 tablets, 72 X 14 tablets, 30 tablets, 100 tablets and 1000 tablets

6.5 Instructions for use, handling and disposal

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

7 Marketing Authorization Holder

Cosmos Limited

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H1983/361

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10 Date of Revision of Text

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