

1. NAME OF THE MEDICINAL PRODUCT

Furosemide Tablets 20mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Furosemide BP 20.0mg.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The treatment of fluid retention associated with Heart failure, including left ventricular failure, cirrhosis of the liver and renal disease including Nephrotic syndrome.

The treatment of mild to moderate hypertension when brisk diuretic response is required. Alone or in combination with other antihypertensive agents in the treatment of more severe cases.

4.2. Posology and method of administration

For oral administration

Adults

The initial adult dose is 40mg daily, reduced to 20mg daily or 40mg on alternate days. In some patients daily doses of 80mg or higher (given in divided doses) may be required.

Children

The usual dose is 1 - 3 mg/kg body weight daily up to a maximum dose of 40mg/day.

Elderly

Caution is advised as furosemide is excreted more slowly in the elderly. Treatment should be started with 20mg and titrated upwards as required.

4.3. Contraindications

Furosemide is contraindicated in the presence of Anuria, Electrolyte deficiency, Precoma associated with Hepatic cirrhosis, Digitalis intoxication, Porphyrria and Hypersensitivity to Furosemide or Sulphonamides.

4.4 Special Warnings and Special Precautions for Use

Furosemide should be discontinued before a glucose tolerance test.

Furosemide should be used with particular caution in elderly patients or those with potential obstruction of the urinary tract or disorders rendering electrolyte balance precarious.

Regular monitoring of fluids and electrolyte balance is recommended. Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy. This may require temporary discontinuation of Furosemide. Regular monitoring of serum sodium, potassium, creatinine and glucose is generally recommended during therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Of note, the risk of electrolyte disturbances can be increased even in mild renal failure.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60ml/min per 1.73m² body surface area as well as in cases where Furosemide is taken in combination with certain other drugs which may lead to an increase in potassium levels.

Particularly careful monitoring is necessary in the following cases :

- Latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- Hepatic failure and alcoholic cirrhosis particularly predispose to hypokalaemia and hypomagnesaemia. (Refer to section 4.8 for details of electrolyte and metabolic abnormalities).
- Use with caution in patients with a history of gout. Furosemide may predispose the patient to the development of hyperuricaemia. (Refer to Section 4.8)
- Patients with hypoproteinaemia, e.g. associated with nephrotoxic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titrated is required.

Use with caution in patients with impaired hepatic, cardiac or renal function, diabetes mellitus or adrenal disease and elderly patients.

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.

Acute diuresis may cause urinary retention in patients with urinary outflow obstruction (such as prostatic hyperplasia/ hypertrophy or impairment of micturition). Urinary output must be monitored in these patients.

Co-administration with nonsteroidal anti-inflammatory analgesics (NSAIDs) should be avoided wherever possible. Where this is not possible, particularly careful monitoring is required to ensure that the diuretic effect is not attenuated (Refer to section 4.5).

Use with caution in patients with hypotension, liver failure, prostate enlargement.

Hypotension may occur if ACE inhibitors are added to Furosemide therapy. The dose of Furosemide should be reduced or the drug stopped before initiating the ACE inhibitor.

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

4.5 Interactions with other Medicinal Products and other Forms of Interaction

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.

A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors or angiotensin II receptor antagonists are added to furosemide therapy, or their dose level increased. The dose of Furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or angiotensin II receptor antagonist or increasing their dose.

Increased risk of hyperkalaemia when furosemide given with: Potassium salts or supplements, potassium-sparing diuretics (such as amiloride and spironolactone), ACE inhibitors, angiotensin receptor antagonists, ciclosporin, tacrolimus, trilostane and drospirinone.

The toxic effects of nephrotoxic drugs like cephaloridine, amphotericine and the aminoglycoside antibiotics may be increased by concomitant administration with potent diuretics such as furosemide . Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Furosemide may reduce the elimination of lithium, 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.

Certain non-steroidal anti-inflammatory agents (e.g. indometacin, acetylsalicylic acid) may attenuate the action of Furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylic toxicity may be increased by furosemide. Furosemide decreases the effects of some drugs (e.g. antidiabetics and pressor amines) and may potentiate the effects of others (e.g. salicylates, theophylline and curare type muscle relaxants).

Concomitant administration of carbamazepine, aminoglutethamide or trimethoprim may increase the risk of hyponatraemia.

Concurrent administration of corticosteroids may cause sodium retention and exacerbate potassium loss.

Amiloride may cause raised blood digoxin levels. Furosemide induced electrolyte disturbances (such as hypokalaemia, hypomagnesaemia) may predispose the patient to arrhythmogenic effect of other drugs (such as digoxin and drugs that prolong the QT interval).

Furosemide may enhance the toxicity of cardiac glycosides by electrolyte disturbances particularly potassium and magnesium.

Attenuation of the effect of Furosemide may occur following concurrent administration of phenytoin.

Corticosteroids, glycyrrizin (contained in liquorice), B₂ sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia. Resultant hypokalaemia may potentiate the cardiac toxicity of certain drugs such as antihistamines and antiarrhythmics.

Potassium depletion that can result from furosemide administration may potentiate digitalis toxicity.

Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of Furosemide. Probenecid may reduce the renal clearance 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.

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins

Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

Furosemide may potentiate the ototoxicity of aminoglycoside and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

4.6. Pregnancy and lactation

Furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxemia of pregnancy without causing foetal or newborn adverse effects. However, it should only be given during pregnancy if strictly indicated and for short-term treatment. As

it may inhibit lactation and passes into breast milk, furosemide should be used with caution in nursing mothers.

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 machines.

4.8 Undesirable Effects

Blood and lymphatic system disorders	Occasionally:	thrombocytopenia
	Rare	bone marrow depression, (necessitates withdrawal of treatment). leucopenia, eosinophilia.
	Very Rare:	agranulocytosis, aplastic anaemia, haemolytic anaemia.
Cardiac disorders	Uncommon	Cardiac arrhythmias
Congenital, familial and genetic disorders	Rare or very rare	Patent ductus arteriosus
Ear and labyrinth disorders	Rare or very rare	Tinnitus, reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly).
Eye disorders	Uncommon	visual disturbance
Gastrointestinal disorders	Uncommon	dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation.
	Rare or very rare	Acute Pancreatitis
General disorders and administration site conditions	Uncommon	Fatigue
	Rare or very rare	Malaise, Fever
Hepato-biliary disorders	Rare or very rare	Pure Intrahepatic Cholestasis, Hepatic function abnormal.
Investigations	Common	creatinine increased, blood urea increased.
	Rare or very rare	Transaminases increased, blood
	Very common or	dehydration, hyponatraemia,

Metabolism and nutrition disorders	common	hypochloremic metabolic alkalosis, hypokalaemia, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene)
	Uncommon	impaired glucose tolerance (by hypokalaemia), hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides
	Very rare	tetany
Musculoskeletal, connective tissue and bone disorders	Uncommon	muscle cramps, muscle weakness
Nervous system disorders	Rare	Paraesthesia, confusion
Psychiatric disorder	Rare	Psychiatric disorder NOC,
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 or very rare	nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure.
Skin and subcutaneous tissue disorders	Rare or very rare	Rash, photosensitivity.
	Ocassionally	Urticaria, purpura, erythema multiforme , exfoliative dermatitis, itching, bullous lesions.
Vascular disorders	Very common or 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 or very rare	Vasculitis, Thrombosis, shock

4.9. Overdose

In cases of overdosage there is a danger of dehydration and electrolyte depletion due to excessive diuresis. Treatment should be aimed at correction of electrolyte imbalance. Gastric lavage may be useful if ingestion is recent.

5.1. Pharmacodynamic properties

ATC code: CO3C A01

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.

The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced and a hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2. Pharmacokinetic properties

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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, Starch, Magnesium Stearate, Povidone, Sodium starch Glycollate.

6.2. Incompatibilities

None known.

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store in a cool dry place protected from light below 25°C.

6.5. Nature and contents of container

Securitainers and/or tampereiner containing 100, 250, 500, or 1000 tablets.
PVC/Al Blister containing 28 tablets.

6.6. Instruction for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 16201/0012

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11/08/2010