Baxter

Baxter Pharmaceuticals India Private Limited

Artwork Code : 1400008098	**Artwork Req. No: 27738**
Quality of Paper/Board : Super Sun Shine	**Size of Artwork (In mm) : 400x175**
Quality of Gum :	**GSM of Paper/Board : 60 GSM**

Colour Code : BLACK ■ | Pantone ☐ | Pantone ☐ | Pantone ☐ | Pantone ☐ | Pantone ☐ | Pantone ☐ | Pantone ☐

Barcode Information:

Barcode Scan Report:

Packing: 2ml Amp	**Plant Location : Injectable**
Country: Israel	**Language : English**
Ref. Code Creation/Blockage Note:	**Artwork Control Key No.:**

"Controlled Copy" Holder (1) (2) (3) (4) (5)

Date: 31/03/21

Furosemide Baxter 20 mg/2 ml Solution for Injection, I.M / I.V use

1. Name of the medicinal product

Furosemide Baxter 20 mg/2 ml

2. Qualitative and quantitative composition

Each ml contains 10 mg of Furosemide.
Each 2 ml ampoule contains 20mg of furosemide
For a full list of excipients, see section 6.1

3. Pharmaceutical form
Solution for injection.
It is clear, colourless or almost colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration
Route of administration: intramuscular or intravenous

Adults

Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine >5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration are feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.

To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide infusion is generally to be preferred to repeated bolus injections. Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals (approx. 4 hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given increasing by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly: The dosage recommendations for adults apply, but in the elderly furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

Children: Parenteral doses for children range from 0.5 to 1.5 mg/kg body weight daily up to a maximum total daily dose of 20 mg.

4.3 Contraindications
Furosemide Baxter 20 mg/2 ml is contraindicated in patients with

- hypovolaemia or dehydration, anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma, severe hypokalaemia, severe hyponatraemia and pre-comatose and comatose states associated with hepatic encephalopathy.
- hypersensitivity to furosemide or any of the excipients of Furosemide Baxter 20 mg/2 ml. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute retention and require careful monitoring.

Steps should be taken to correct hypovolaemia before commencing therapy in oliguria.

Caution is required in patients with liver failure, porphyria, pancreatitis or a history of pancreatitis, systemic lupus erythematosus or a history of systemic lupus erythematosus or severe asthma (hypokalaemia associated with beta2-agonist therapy can be potentiated by the concurrent use of diuretics). The insulin requirements of diabetic patients may increase on treatment with furosemide and latent diabetes may become manifest.

Particularly careful monitoring is necessary in:

- patients with hypotension- correct before use.
- patients who are at risk from a pronounced fall in blood pressure.
- patients with gout
- patients with hepatorenal syndrome
- patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated).

Cautious dose titration is required.

- premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

Caution should be observed in patients liable to electrolyte deficiency such as elderly. The risk of hypokalaemia is increased in patients with severe or congestive heart failure, hepatic cirrhosis or hyperaldosteronism. 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.

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

Prolonged treatment with furosemide can lead to thiamine deficiency, particularly in congestive heart failure or the elderly.

This medicinal product contains 7.5 mg of sodium in a 2 ml ampoule. To be taken into consideration by patients on a controlled sodium diet.

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

Concomitant use with risperidone

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Enhanced hypotensive effect. Orthostatic hypotension, associated with diuretics, may be enhanced.

Aldesleukin: Enhanced hypotensive effect.

Anaesthetics, general: Enhanced hypotensive effects.

Anion-exchange resins: Colestyramine and colestipol markedly reduce the absorption of furosemide. Administer two to three hours apart.

Anti-arrhythmics: Toxicity of amiodarone, disopyramide, flecainide and quinidine is increased if hypokalaemia occurs. Action of lidocaine and mexilitine is antagonised by hypokalaemia.

Hypokalaemia increases risk of ventricular arrhythmias with sotalol, a beta-blocker.

Antibacterials: Furosemide may enhance the toxicity of nephrotoxic antibiotics including some cephalosporins. It can enhance the ototoxicity of aminoglycoside antibiotics, vancomycin and other ototoxic agents. Since this may lead to permanent damage, these drugs must only be used with furosemide if there are compelling medical reasons.
Anticoagulants: Reduced anticoagulant effect when furosemide used concomitantly with warfarin.

Antidepressants: Increased risk of postural hypotension with tricyclic antidepressants. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Increase risk of hypokalaemia when furosemide and reboxetine are used concomitantly.

Antidiabetics: The hypoglycaemic effect is antagonised by loop diuretics.

Antiepileptics: Increased risk of hyponatraemia with concomitant carbamazepine. The diuretic effect of furosemide has been shown to be substantially reduced by concomitant phenytoin therapy.

Antifungals: Increased risk of hypokalaemia with loop diuretics and amphotericin.

Anti-gout: Probenecid has been shown to reduce the renal clearance of furosemide and may increase, decrease or have no effect on the overall diuresis. Furosemide may reduce the renal clearance of probenecid. In case of high-dose treatment (with furosemide and probenecid), this may lead to increased serum levels and an increased risk of adverse effects.

Antihistamines: Hypokalaemia increases risk of ventricular arrhythmias with terfenadine.

Antihypertensives: Furosemide enhances the hypotensive action of other antihypertensive drugs, including beta-blockers, calcium-channel blockers and hydralazine. The dosage of currently administered antihypertensive agents may require adjustment. There is an increase risk of firstdose hypotension with alpha blockers such as prazosin or angiotensin-converting enzyme (ACE) inhibitors such as captopril. Particular care should be taken with ACE inhibitors and angiotensin-II antagonists when initiating or increasing their dose in concomitant therapy with furosemide, since combination can result in marked reduction in blood pressure and deterioration in renal function. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating or increasing the dose of an ACE inhibitor or angiotensin II receptor antagonist. Long term intensive treatment with captopril can enhance the natriuretic response to furosemide.

Antipsychotics: Hypokalaemia increases risk of ventricular arrhythmias with primozide and sertindole, concurrent use should be avoided. Enhanced hypotensive effect with phenothiazines.

Risperidone: Caution should be exercised and the risks and benefits of the combination or cotreatment 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.

Anxiolytics and hypnotics: Administration of chloral hydrate followed by intravenous furosemide may result in a syndrome of hot flushes, sweating, tachycardia and hypertension.

Cardiac Glycosides: Increased risk of toxicity if hypokalaemia or hypomagnesaemia occurs. The cardiac glycoside dosage may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.

Corticosteroids: The increased risk of hypokalaemia occurs particularly with the naturally occurring corticosteroids such as cortisone and hydrocortisone. The synthetic corticosteroids have a much less marked potassium-losing effect. Fluid retention associated with corticosteroid use may cause antagonism of diuretic/antihypertensive effect. Concomitant administration of corticosteroids may cause sodium retention.

Cytotoxics: 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. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced dieresis during cisplatin treatment.

Diuretics: Increased risk of hypokalaemia with other loop diuretics and other diuretics, including acetazolamide and thiazides. Severe electrolyte disturbances may occur in patients given metolazone concurrently with furosemide. The dosage of concurrently administered diuretics may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.

Dompaminergics: Enhanced hypotensive effect with levodopa.

Immunosuppressants: Ciclosporin: concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

Laxatives: Prolonged use may increase the risk of developing hypokalaemia.

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. It is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Muscle relaxants: Enhanced hypotensive effect may occur with tizanidine; effects of curare-type muscle relaxants may be potentiated.

Nicotine: Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide.

Nitrates: Enhanced hypotensive effect.

Non-steroidal anti-inflammatory agents (NSAIDs): Certain non-steroidal anti-inflammatory agents (e.g. indometacin, ketorolac, acetylsalicylic acid) may attenuate the diuretic effect of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Enhanced salicylate toxicity or nephrotoxicity of NSAIDs.

Prostaglandins: Hypotensive effect may be potentiated by alprostadil.

Sympathomimetics: There is an increased risk of hypokalaemia with high doses of β2- sympathomimetics. Effects of pressor amines may be attenuated.

Theophylline: Risk of hypokalaemia may be increased; effects of theophylline may be potentiated.

Ulcer healing drugs: carbenoxolone and liquorice may increase risk of hypokalaemia. Fluid retention associated with carbenoxolone may cause antagonism of diuretic/antihypertensive effect.

Ranitidine causes a moderate increase in the bioavailability of furosemide.

4.6 Pregnancy and lactation

Animal teratology studies indicate that furosemide may cause foetal abnormalities. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, furosemide crosses the placental barrier. As furosemide is a potent diuretic, reduction in maternal blood volume following administration could compromise placental perfusion. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Furosemide passes into breast milk and may inhibit lactation. Furosemide is not recommended in nursing mothers.

4.7 Effects on ability to drive and use machines

Reduced mental alertness may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects

Furosemide 10mg/ml Injection is generally well tolerated.

Metabolism and nutrition disorders: The most common side-effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, hypochloraemic alkalosis, hypotension and increased calcium excretion.

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 water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide

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doses are administered to patients with normal renal function, acute severe electrolyte losses.
Warning signs of electrolyte disturbances include increased thirst, dry mouth, headache, hypotension, drowsiness, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms.

Increased calcium excretion in infants and new-borns has been associated with reports of decreased bone mineral content, rickets, fractures and renal calcification. Hypocalcaemic tetany has also been reported in hypoparathyroid patients. Nephrocalcinosis / Nephrolithiasis may develop in premature infants.

Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

Thiamine deficiency with prolonged treatment, particularly in congestive heart failure and the elderly.

Furosemide may cause hyperuricaemia and precipitate attacks of gout in some patients.

Serum cholesterol and triglyceride levels may rise during furosemide treatment. During long term therapy they will usually return to normal within six months.

Nervous system disorders: Syncope, rarely, paraesthesiae may occur.

Ear and labyrinth disorders: tinnitus and deafness, although usually transitory, may occur in rare cases, (usually with large parenteral doses and rapid administration or in patients with hypoproteinaemia or renal impairment). Rarely deafness may be permanent, particularly if furosemide has been given to patients taking other ototoxic drugs.

Eye disorders: Blurred vision, yellow vision.

Vascular disorders: Furosemide may cause a reduction in blood pressure which, if pronounced, may cause signs and symptoms such as impairment of concentration and reactions, lightheadedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic hypotension. 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.

Immune system disorders: Hypersensitivity reactions, that may include skin rashes, photosensitivity, vasculitis, fever, urticaria and interstitial nephritis occur rarely but when these occur treatment should be withdrawn. Severe anaphylaxis or anaphylactoid reactions (e.g with shock) may also occur rarely and necessitate immediate withdrawal of furosemide treatment.

Endocrine disorders: Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control with hyperglycaemia and glycosuria; latent diabetes mellitus may also become manifest.

Gastrointestinal disorders: side-effects of a minor nature such as nausea, or gastric upset (vomiting and diarrhoea) may occur but are not usually severe enough to necessitate withdrawal or treatment. Pancreatitis is more common at high doses.

Blood and lymphatic system disorders: In rare cases, thrombocytopenia, leucopenia, agranulocytosis, eosinophilia, aplastic anaemia or haemolytic anaemia may develop. Bone marrow depression necessitates withdrawal of treatment.

Hepatobiliary disorders: In isolated cases, intrahepatic cholestasis, an increase in liver transaminases, or cholestatic jaundice has been reported. Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.

Pregnancy, puerperium and perinatal conditions: If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Renal and urinary disorders: 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. As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels.

Skin and subcutaneous tissue disorders: Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticarial, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, purpura, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).

General disorders and administration site conditions: malaise. Following intramuscular injection, local reactions such as pain may occur.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Symptoms:

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.

Treatment:

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-Ceiling Diuretics

ATC code: C03CA01

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 Henle 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

Sodium Chloride
Sodium Hydroxide
Hydrochloric Acid
Water for injections

6.2 Incompatibilities

Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions).

Furosemide Baxter 20mg/2ml may be mixed with neutral and weak alkaline solution with pH between 7 and 10, such as:

0.9%w/v Sodium Chloride solution

0.9%w/v Sodium Chloride and 5%w/v glucose solution

Compound sodium lactate intravenous infusion

After dilution: chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25º c. Protect from light.

6.5 Nature and contents of container

Furosemide Baxter 20 mg/2 ml Injection is available as 2 ml glass ampoules containing 2 ml of solution.
5 Glass Ampoules are packed in 1 Open Tray Blister.

1) Such 1 Tray is packed in 1 carton with leaflet- Pack of 5
2) Such 2 Tray is packed in 1 carton with leaflet- Pack of 10
3) Such 3 Tray is packed in 1 carton with leaflet- Pack of 25

* Not all pack size may be marketed

6.6 Special precautions for disposal and other handling

None

7. Manufacturer

Baxter Pharmaceuticals India Private Limited
Vasana-Chacharwadi,
Ahmedabad-382 213, India.

8. Marketing authorisation holder

David Margalit & Co. Ltd.
P.O Box 16666, Tel Aviv 6116601

9. Marketing authorisation number

157-93-34378

Revised in March 2021

1400008098