pharmaniaga®

Furosemide 20mg/2ml Injection

DESCRIPTION
Clear, colourless solution.

COMPOSITION
Each 2mL contains Furosemide 20mg.

PHARMACODYNAMICS
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.

PHARMACOKINETICS
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.

INDICATION
Furosemide 20mg/2ml Injection is indicated in adults, infants and children for the treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease including the nephrotic syndrome.

Furosemide 20mg/2ml Injection is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired. Parenteral therapy should be reserved for patients unable to take oral medication or for patients in emergency clinical situations.

Furosemide 20mg/2ml Injection is also indicated as adjunctive therapy in acute pulmonary oedema and cerebral oedema where intense and rapid onset of diuresis is desired. If gastrointestinal absorption is impaired or oral medication is not practical for any reason, Furosemide is indicated by the intravenous route.
Parenteral use should be replaced with oral Furosemide as soon as practical.

RECOMMENDED DOSAGE
Adults
Parenteral administration: Parenteral administration of furosemide should be reserved for patients in whom oral medication is not recommended. Parenteral therapy should be replaced with oral therapy, as soon as this is practical, for the continued mobilisation of oedema. The usual initial dose of furosemide is 20 to 40 mg given as a single dose, injected intramuscularly or intravenously. The intravenous injection should be given slowly (1 to 2 minutes). Ordinarily a prompt diuresis ensues. Depending on the patients response a second dose can be administered two hours after the first dose, or later.

If the diuretic response with a single dose of 20 to 40 mg is not satisfactory: e.g. In a patient refractory to maximal doses of thiazides, the following schedule should be used under careful medical supervision: increase this dose by increments of 20 mg, not sooner than two hours after the previous dose, until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily.

Acute pulmonary oedema: Since the diuresis evoked by furosemide given intravenously commences within five minutes and leads to an intensive diuresis, the use of furosemide intravenously in the treatment of patients with acute pulmonary oedema has proven particularly valuable. The following schedule is recommended: 40 mg of furosemide is immediately injected slowly, intravenously followed by another 40 mg dose. 1 to 1½ hours later if that is indicated by the patient's condition. If deemed necessary additional therapy (e.g. digitalis, oxygen) can be administered concomitantly.

Infants and children
Paediatric administration: Parenteral administration of furosemide should be reserved for patients in whom oral medication is not recommended. Parenteral therapy should be replaced by oral therapy as soon as this is practical, for continued mobilisation of oedema. For maintenance therapy in infants and children the dose should be adjusted to the minimum effective level. The usual initial dose of furosemide injection (intravenously or intramuscularly) in infants and children are 1 mg/kg body weight and should be given under close medical supervision. If the diuretic response after the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than two hours after the previous dose, until the desired effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended.

CONTRAINDICATIONS
Furosemide 20mg/2ml Injection is contra-indicated 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 20mg/2ml Injection. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

WARNING AND PRECAUTION
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 $beta_2$- 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 nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated).

Cautious dose titration is required.
• premature infants and neonates (possible development of nephrocalcinosis /nephrolithiasis in association with increased calcium excretion during long-term furosemide treatment; renal function must be monitored and renal ultrasonography performed)

Caution should be observed in patients liable to electrolyte deficiency such as the 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 0.26mmol of sodium in a 2ml 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:
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.

Effects on ability to drive and use machines:
Reduced mental alertness may impair ability to drive or operate dangerous machinery.

INTERACTIONS WITH OTHER MEDICAMENTS

- 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.
- Antihistamines: Hypokalaemia increases risk of ventricular arrhythmias with terfenadine.
- Antihypertensives: Furosemide enhances the hypotensive action of other antihypertensive drugs, including betablockers, calcium-channel blockers and hydralazine. The dosage of currently administered antihypertensive agents may require adjustment. There is an increase risk of first-dose 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, since combination with furosemide can result in marked reduction in blood pressure. 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. 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.
- 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 occurs.

- Corticosteroids: There is increased risk of hypokalaemia 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.

- 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.

- Dompaminergics: Enhanced hypotensive effect with levodopa.

- 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. Therefore, 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) may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Enhanced 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.

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

STATEMENT ON USAGE DURING 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.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Furosemide 20mg/2ml 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 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, light-headedness, 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, urticaria, and other rashes. Rarely these may be severe and may include purpura and exfoliative dermatitis and bullous lesions such as erythema multiforme and pemphigoid.

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

OVERDOSAGE
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 those designed to reduce absorption (e.g. activated charcoal).

STORAGE CONDITION
Store below 30°C. Protect from light.
Do not use if solution contains particles, growth, turbidity or if there is any change of appearance.

SHELF-LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORM AND PACKAGING AVAILABLE
Injection - 10 x 2ml ampoule (amber)

REGISTRATION NUMBER
MAL 15045138AZ

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