For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Steril-Gene Furosemide Injection BP 20mg/2ml Solution for Injection or infusion

(For I.M/I.V use)

Composition : Each 2ml contains:
Furosemide BP..... 20mg
Water for Injections BP....q.s.

Product Description
A clear and colorless solution free from visible particulate filled in 2ml ampoule. pH of the solution is between 8.00 to 9.30.

Indications
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, Frusemide is indicated by the intravenous route.
Parenteral use should be replaced with oral Frusemide as soon as practical.

Dosage and Administration:
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 intrvenously 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.

Instruction for Use
Intravenous Furosemide must be injected or infused slowly; When administered as an infusion, Furosemide may be administered undiluted using a constant-rate infusion pump. 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 administrations 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.

Pharmacodynamic
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.

Pharmacokinetic
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 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.

Contraindications

Furosemide 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, pre-comatose and comatose states associated with hepatic encephalopathy and breast feeding women. Hypersensitivity to furosemide or any of the excipients of Frusemide. 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.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Particularly careful monitoring is necessary in:

• Patients with hypotension.

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

• Patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.

• 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. 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.

In patients who are at high risk for radiocontrast nephropathy, Furosemide is not recommended to be used for duiresis 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 Machine

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

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.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of 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.
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 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.
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.
Certain non-steroidal anti-inflammatory agents (e.g. indomethacin, acetylsalicylic acid) may attenuate the action of Furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Salicylate toxicity may be increased by Furosemide. Furosemide may sometimes attenuate the effects of other drugs (e.g. the effects of anti-diabetics and of pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline and curare-type muscle relaxants).
Furosemide may potentiate the ototoxicity of aminoglycosides 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.
Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).
Attenuation of the effect of Furosemide may occur following concurrent administration of phenytoin. Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.
Corticosteroids administered concurrently may cause sodium retention.
Corticosteroids, carbenoxolone, liquorice, B2 sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.
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.
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.

Important incompatibilities
Furosemide should not be mixed with any other medication in the same syringe. Furosemide produces a precipitate when mixed with Dobutamine, Diazepam, Doxorubicin, Droperidol, Gentamicin, Glucose, Mannitol, Metoclopramide, Potassium Chloride, Tetracycline, Vincristine and Vitamins.

It should not be given during infusion with Adrenaline, Isoprenaline, Lidocaine or Pethidine.

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 foetal growth.
Furosemide passes into breast milk and may inhibit lactation. Women must not breast-feed if they are treated with Furosemide.

Undesirable effects
Furosemide is generally well tolerated. Eosinophilia is rare. Occasionally, thrombocytopenia may occur. In rare cases, leucopenia and, in isolated cases, agranulocytosis, aplastic anaemia or haemolytic anaemia may develop.

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment. Rarely, paraesthesiae may occur.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur. Serum calcium levels may be reduced; in very rare cases tetany has been observed. Nephrocalcinosis / Nephrolithiasis has been reported in premature infants.

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

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.

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.

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.

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

The incidence of allergic reactions, such as skin rashes, photosensitivity, vasculitis, fever, interstitial nephritis or shock is very low, but when these occur treatment should be withdrawn. Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, 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).

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, headache, hypotension, confusion, muscle cramps, tetany, muscle weakness, disorders of cardiac rhythm and gastrointestinal symptoms. Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by Furosemide treatment.

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.

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. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely. Side-effects of a minor nature such as nausea, malaise or gastric upset (vomiting or diarrhoea) may occur but are not usually severe enough to necessitate withdrawal of treatment.

Following intramuscular injection, local reactions such as pain may occur. As with other diuretics, treatment with furosemide may lead to transitory increases in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

Overdose and Treatment
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 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).

Storage condition
Store below 30°C. Protect from light. Keep out of reach of children.

Availability
Steril-Gene Furosemide Injection BP 20mg/2ml Solution for Injection or infusion (For I.M./I.V use) is available as 10×2mL amber ampoule USP type 1.

Manufactured in India by:
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