

## **1. NAME OF THE MEDICINAL PRODUCT**

Furosemide Injection BP 250mg/25ml.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 1ml of sterile solution for infusion contains Furosemide 10mg.

Each 25ml ampoule contains Furosemide 250mg

Excipient: each 1ml contains 3.64mg (0.16mmol) sodium

For full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for infusion.

Clear, colourless or almost colourless sterile solution.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

As a diuretic in the management of oliguria due to acute or chronic renal insufficiency with a GFR below 20ml/minute.

### **4.2 Posology and method of administration**

Route of administration: intramuscular or intravenous

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.

The recommended initial dose is one 25ml ampoule (250mg) diluted in 225ml Sodium Chloride Injection BP or Ringer's solution for injection, administered over one hour. If urine output is insufficient within the next hour, a dose of two 25ml ampoules (500mg) in an appropriate infusion fluid may be given over two hours. The total volume of the infusion should be governed by the patient's state of hydration. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion, a third infusion containing four 25ml ampoules (1,000mg) may be given. The rate of infusion should not exceed 4mg/minute.

In oliguric or anuric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant-rate infusion pump with a micrometer screw-gauge adjustment; the rate of administration should still not exceed 4mg/minute. If the response to either method of administration is satisfactory, then the effective dose (of up to 1g) may be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, the oral route may be used for maintenance therapy and 500mg may be given by mouth for each 250mg required by injection. Patients who do not respond to a third infusion, using the maximum intravenous dose of 1g over four hours, probably require dialysis.

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. Doses for children can only be determined on the basis of the severity of the renal insufficiency and the clinical response to initial doses.

### **4.3 Contraindications**

Furosemide 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, pre-comatose and comatose states associated with hepatic encephalopathy and breast feeding women. Pre-coma associated with hepatic cirrhosis, Addison's disease.

Hypersensitivity to furosemide or any of the excipients of Furosemide Injection BP 250mg/25ml. 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.

During treatment with high-dose forms of furosemide therapy, careful laboratory control is essential. Fluid and electrolyte balance should be carefully controlled. Serum electrolytes should be checked regularly, especially sodium, potassium, chloride and bicarbonate levels, and electrolyte replacement therapy instituted as appropriate.

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. Infusion rates in excess of 4mg/minute are associated with an increased risk of ototoxicity, usually reversible hearing loss.
- 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. Particular care is required when treating elderly patients, or with disorders rendering their electrolyte balance precarious.

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.

Bone marrow depression has been reported as a rare complication and necessitates withdrawal of treatment. The haemopoietic state should, therefore, be monitored regularly during use.

Use with caution in patients with prostate enlargement & porphyria.

#### **4.5 Interactions with other medicinal products and other forms of interactions**

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.

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. 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.

Increased anticoagulant activity is observed when furosemide is co-administered with anticoagulants.

Corticotrophin cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide.

#### **4.6 Pregnancy and lactation**

Furosemide crosses the placenta and is excreted in breast milk. There is no evidence of a teratogenic effect in animal studies. Experience of use in human pregnancy does not to date suggest evidence of teratogenesis. However, furosemide should only be used in pregnancy if considered essential by the physician and should be avoided in women who are nursing infants.

#### **4.7 Effects on ability to drive and use machines**

No known effects on ability to drive and use machines.

#### **4.8 Undesirable effects**

##### **Metabolism and nutrition disorders**

- Increased excretion of sodium and chloride and consequently water.
- Increased excretion of other electrolytes (in particular potassium, calcium and magnesium). Symptomatic electrolyte disturbances and metabolic alkalosis.
- Hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.
- Transitory increases in blood creatinine and urea levels.
- Increase in cholesterol and triglyceride serum levels.
- Increase in uric acid serum levels and attacks of gout.
- Decrease of glucose tolerance.

##### **Vascular Disorders**

- Hypotension including orthostatic hypotension.
- Tendency for thromboses.
- Vasculitis.

##### **Renal and urinary disorders**

- Acute retention of urine in patients with a partial obstruction of urinary outflow
- Interstitial nephritis.
- Nephrocalcinosis/nephrolithiasis in premature infants.

##### **Gastrointestinal disorders**

- Nausea, vomiting, diarrhoea.
- Acute pancreatitis.

##### **Hepatobiliary disorders**

- Intrahepatic cholestasis, increase in liver transaminases.

##### **Ear and labyrinth disorders**

- Hearing disorders, tinnitus.

##### **Skin and subcutaneous tissue disorders**

- Itching, urticaria, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, exfoliative dermatitis, purpura, photosensitivity.

##### **Immune system disorders**

- Severe anaphylactic or anaphylactoid reactions.

## **Nervous system disorders**

- Paraesthesiae.
- Hepatic encephalopathy in patients with hepatocellular insufficiency.

## **Blood and the lymphatic system disorders**

- Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
- Eosinophilia.
- Haemoconcentration.

## **Congenital and familiar/genetic disorders**

- Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

## **General disorders and administration site conditions**

- Following intramuscular injection, local reactions such as pain.
- Fever.

## **4.9 Overdose**

In overdosage, excessive diuresis may lead to hypotension, dehydration and electrolyte depletion. If overdosage occurs, treatment should be directed to correcting dehydration and electrolyte depletion.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Furosemide is a potent diuretic which acts primarily by inhibiting electrolyte absorption in the loop of Henle.

### **5.2 Pharmacokinetic properties**

Following intravenous administration, diuresis occurs within 5 minutes, reaches a maximum within 20 – 60 minutes and persists for approximately 2 hours. Furosemide is strongly bound to plasma proteins and is excreted mostly unchanged through the kidneys. The main site of action is the ascending limb of the loop of Henle.

### **5.3 Preclinical safety data**

No further information other than that which is contained in other sections of the Summary of product characteristics

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium Chloride  
Sodium Hydroxide  
Water for Injections

## **6.2 Incompatibilities**

Furosemide may precipitate in solutions of low pH and therefore, Dextrose solutions are not suitable infusion fluids for Furosemide Injection. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

Unopened: 3 years.

If only part used, discard the remaining solution.

## **6.4 Special precautions for storage**

Do not store above 25°C.

Keep the ampoules in the outer carton in order to protect from light.

Do not refrigerate or freeze.

## **6.5 Nature and contents of container**

25ml, amber glass ampoules, glass type 1 Ph Eur borosilicate glass, packed in cardboard cartons to contain 10 x 25ml ampoules.

## **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

For single use only. If only part used, discard the remaining solution.

## **7. MARKETING AUTHORIZATION HOLDER**

Antigen Pharmaceuticals Ltd.,  
Roscrea,  
County Tipperary,  
Ireland.

## **8. MARKETING AUTHORIZATION NUMBER**

PA 73/59/6

## **9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION**

28th May 1990 / 28th May 2000

## **10. DATE OF (PARTIAL) REVISION OF THE TEXT**

June 2009