

## **PRODUCT SUMMARY**

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

Furosemide Injection B.P. 10mg/ml, 2ml, 5ml & 25ml.

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

Each 1ml of solution contains 10mg of Furosemide B.P.

### **3. PHARMACEUTICAL FORM**

Colourless or almost colourless sterile solution intended for parenteral administration to human beings.

### **4. CLINICAL PARTICULARS**

#### **4.1. Therapeutic Indications**

Furosemide is a potent diuretic and is recommended for use when prompt and effective diuresis is required.

Furosemide Injection B.P. 20mg/2ml and 50mg/5ml are appropriate for use in emergencies or where oral therapy is not feasible. The indications include cardiac, pulmonary, hepatic and renal oedema.

Furosemide Injection B.P. 250mg/25ml is for use in the management of oliguria due to acute or chronic renal insufficiency with a glomerular filtration rate below 20ml/minute.

#### **4.2. Posology and Method of Administration**

Furosemide Injection B.P. 20mg/2ml and 50mg/5ml are for intramuscular or for intravenous administration and must always be given slowly. Furosemide Injection B.P. 250mg/25ml is for slow intravenous administration.

Furosemide Injection B.P. 20mg/2ml and 50mg/5ml

*Adults* : Initially, doses of 20 - 50mg may be administered by the intramuscular route, or by slow intravenous injection at a rate not exceeding

4mg/minute. The diuretic effect of furosemide is proportional to the dosage and, if larger doses are required, they should be given as a controlled infusion at a rate not exceeding 4mg/minute and titrated according to the response.

*Elderly* : Elimination of furosemide is generally slower in the elderly. Dosage should be titrated until the required effect is achieved.

*Children* : Dosages for children range from 0.5 - 1.5mg/kg weight daily up to a maximum total daily dose of 20mg.

#### Furosemide Injection B.P. 250mg/25ml

*Adults* : Furosemide Injection B.P. 250mg/25ml is for slow intravenous injection at a rate not exceeding 4mg/minute.

An initial dose of 250mg (one 25ml ampoule) may be added to about 225ml Sodium Chloride Injection B.P. or Ringer's Solution for Injection, and infused over one hour at a drip rate of 80 drops/minute (4mg/minute).

If urine output within the next hour is insufficient, a dose of 500mg (two 25ml ampoules) in an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, may be infused at a rate not exceeding 4mg/minute. If a satisfactory urine output has still not been achieved within one hour following the end of the second infusion, a third dose consisting of 1,000mg (four 25ml ampoules) in an appropriate infusion fluid may be given. The rate of infusion should never exceed 4mg/minute.

If the third infusion (1,000mg over 4 hours) is not effective, dialysis will probably be required.

In oliguric or anuric patients with significant fluid overload, it may not be practicable to use the aforementioned method of administration. In such cases, the use of a constant-rate infusion pump with a micrometer screw-gauge adjustment may be considered for direct administration of the injection into the vein. The rate of infusion should still never exceed 4mg/min.

If the response to either method of administration is satisfactory (urine output 40 - 50ml/hour), the effective dose (of up to 1,000mg) may be repeated every 24 hours. Alternatively, treatment may be maintained by oral administration of Furosemide Tablets, using 500mg by mouth for each 250mg required by injection. Appropriate adjustments to dosage may then be made according to the patient's response.

*Elderly* : Elimination of furosemide is generally slower in the elderly. Dosage should be titrated until the required effect is achieved.

*Children* : Dosages for children must be determined on the basis of the severity of the renal insufficiency and on the clinical response to initial doses.

### 4.3 Contraindications

- Hypersensitivity to furosemide or any of the excipients of this product.
- Hypersensitivity to sulphonamides or sulphonamide derivatives (because of cross-sensitivity between sulphonamides and furosemide).
- Patients with hypovolaemia or dehydration (with or without accompanying hypotension).
- 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.
- Pre-comatose and comatose states associated with hepatic encephalopathy.
- Severe hypokalaemia, severe hyponatraemia.
- Addison's disease
- Breast feeding women.
- Porphyria

### 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. 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 diuresis as part of the preventative measures against radiocontrast-induced nephropathy. Intravenous administration rate should not usually exceed 4 mg/minute, however single doses of up to 80 mg may be administered more rapidly; a lower infusion rate may be considered in those with renal impairment.

#### 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 (see section 4.3 Contraindications).

#### **4.5 Interactions with other Medicinal Products and other forms of interaction**

The dosage of concurrently administered cardiac glycosides, diuretics, antihypertensive 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.

Enhanced hypotensive effect when diuretics are given with adrenergic neurone blockers, diazoxide, sodium nitroprusside, aldesleukin, alprostadil, general anaesthetics, anxiolytics and hypnotics, baclofen, clonidine, hydralazine, levodopa, MAOIs, methyl dopa, minoxidil, moxislyte, moxonidine, phenothiazines, tizanidine, prazosin, beta blockers and calcium channel blockers.

There is increased risk of postural hypotension when diuretics given with tricyclics

The toxic effects of nephrotoxic drugs like cephaloridine, amphotericin 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. Diuretics increase risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect.

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, and curare type muscle relaxants).

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.

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).

Concomitant administration of carbamazepine may increase the risk of hyponatraemia.

Concurrent administration of corticosteroids may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, B<sub>2</sub> sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

Increased risk of hypokalaemia when loop diuretics are given with acetazolamide, theophylline

Potassium depletion that can result from furosemide administration may potentiate digitalis toxicity. Hypokalaemia caused by loop diuretics increases cardiac toxicity with amiodarone, disopyramide, flecainide. Hypokalaemia caused by loop diuretics antagonises action of lidocaine (lignocaine).

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

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.

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. See section 4.4 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

#### **4.6 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. Furosemide should not be used to treat gestational hypertension.

#### **4.7. Effects on Ability to Drive and Use Machines**

In patients receiving diuretics, some reduction in mental alertness may impair ability to drive or to operate machinery.

#### **4.8 Undesirable effects**

Adverse reactions reported for furosemide are given below according to organ systems. The frequencies of the adverse reactions are classified as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reactions- Frequency Category
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	Rare ( $\geq 1/10,000$ to $< 1/1,000$ )	Very Rare ( $< 1/10,000$ )	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders	Eosinophilia, Leucopenia, Bone marrow depression		Thrombocytopenia, Agranulocytosis, Aplastic anaemia, Haemolytic anaemia
Immune system disorders	Severe anaphylactic or anaphylactoid reactions (e.g. with shock)		Photosensitivity, Interstitial nephritis, Vasculitis
Metabolism and nutrition disorders			Electrolyte and water imbalance <sup>1</sup> , Hyponatraemia, Hypokalaemia, Hypochloraemia, Hypomagnesaemia, Metabolic alkalosis, Hypovolaemia <sup>2</sup> , Dehydration, Increase in serum cholesterol and triglyceride levels <sup>3</sup> , Decrease in glucose tolerance <sup>4</sup> , Hyperuricaemia, Gout
Nervous system disorders	Paraesthesia		Impairment of concentration and reactions, Light-headedness, Sensations of pressure in the head, Headache, Dizziness, Drowsiness, Weakness, Confusion
Eye disorders			Disorders of vision
Ear and labyrinth disorders	Hearing disorders, Tinnitus		
Cardiac disorders			Disorders of cardiac rhythm, Persistence of patent ductus arteriosus (in premature infants)
Vascular			Hypotension, Orthostatic intolerance

disorders			
Gastrointestinal disorders			Nausea, Vomiting, Diarrhoea, Dry mouth, Thirst
Hepatobiliary disorders			Intrahepatic cholestasis, Increase in liver transaminases, Acute pancreatitis, Hepatic encephalopathy
Skin and subcutaneous tissue disorders			Itching, Urticaria, Skin rashes, Bullous lesions, Erythema multiforme, Bullous pemphigoid, Stevens-Johnson Syndrome, Toxic epidermal necrolysis, Exfoliative dermatitis, Purpura
Musculoskeletal and connective tissue disorders		Tetany	Muscle cramps, Muscle weakness, Hypocalcaemia
Renal and urinary disorders			Increase in blood creatinine and urea levels, Increased production of urine , Nephrocalcinosis / Nephrolithiasis (in premature infants)
General disorders and administration site conditions			Malaise, Fever, Pain at injection site

*Additional information*

<sup>1</sup>Electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. 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.

<sup>2</sup>Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

<sup>3</sup>During long term therapy they will usually return to normal within six months.

<sup>4</sup>In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest.

#### *Paediatric population*

Nephrocalcinosis / Nephrolithiasis has been reported in premature infants. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

#### *Other special populations*

##### *Elderly patients*

The diuretic action of furosemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients.

##### *Patients with hepatic impairment*

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).  
Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

##### *Patients with renal impairment*

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. 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.

## **4.9 Overdose**

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).

## **5.1 Pharmacodynamic properties**

ATC code: CO3C A01

Furosemide is a potent diuretic. It is an anthranilic acid derivative and chemically it is 4-chloro-N-furfuryl-5-sulphamoylanthranilic acid. Furosemide inhibits the reabsorption of sodium and chloride in the loop of Henle as well as in the proximal and distal tubules; its action is independent of any inhibitory effect on carbonic anhydrase. The urinary excretion of potassium, calcium and magnesium is increased by furosemide. Hyperuricaemia may occur and is presumed to result from a competitive inhibition of urate secretion in the proximal tubules.

Furosemide has a steep dose-response curve and is designated a high-ceiling diuretic. Following intravenous administration, the onset of diuresis is within 5 minutes and the duration of diuretic effect is approximately two hours.

## **5.2 Pharmacokinetic properties**

Furosemide is extensively bound to plasma proteins and is mainly excreted in the urine, largely unchanged. Furosemide glucuronide is the main biotransformation product.

Furosemide has a biphasic half-life in patients with a terminal elimination phase of approximately 1.5 hours. Although mainly excreted in the urine, variable amounts are also excreted in bile and non-renal elimination may be considerably increased in renal failure.

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 Injection, 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. Pre-clinical Safety Data**

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of Excipients**

Sodium Chloride B.P.  
Sodium Hydroxide B.P.  
Water for Injections B.P.

### **6.2. Incompatibilities**

Furosemide may precipitate solutions of low pH, and therefore dextrose solutions are not suitable infusion fluids for furosemide injection. The injection solution should not be mixed with other drugs in infusion bottles.

### **6.3. Shelf-Life**

3 years (36 months).  
If only part used, discard the remaining solution.

### **6.4 Special precautions for storage**

Keep in outer carton  
Do not store above 25°C  
Do not refrigerate or freeze.

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

2ml, 5ml & 25ml One point cut (OPC) amber glass ampoules, glass type 1 Ph.Eur.  
packed in cardboard cartons to contain 10 x 2ml or 10 x 5ml or 10 x 25ml ampoules

### **6.6. Instructions for Use, Handling and Disposal**

Not applicable.

**ADMINISTRATIVE DATA**

**7.     MARKETING AUTHORISATION HOLDER**

Antigen International Ltd.,  
Roscrea,  
Co. Tipperary,  
Ireland.

**8.     MARKETING AUTHORISATION NUMBER(S)**

PL 2848/0103.

**9.     DATE OF FIRST AUTHORISATION / RENEWAL OF  
AUTHORISATION**

24 September 1990 / 18 July 1997.

**10    DATE OF REVISION OF THE TEXT**

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