

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 20mg in 2ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml ampoule contains Furosemide 20mg.

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless or almost colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a diuretic in the treatment of fluid retention.

4.2 Posology and method of administration

Furosemide 20mg in 2ml Solution for Injection is for intramuscular or slow intravenous administration.

Adults: The usual initial dose in adults is 20 to 50mg, administered by intramuscular injection or by slow intravenous injection at a rate not exceeding 4mg/minute. A second dose may be given not less than 2 hours later, according to the patient's response.

Elderly: Furosemide is generally eliminated more slowly in the elderly. Dosage should be titrated until the required response is achieved.

Children: For children, the suggested dose is 0.5 to 1.5mg/kg body weight daily.

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

Too vigorous diuresis may cause orthostatic hypotension or acute hypotensive episodes.

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

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.

Urinary output must be secured. In patients with a partial obstruction of urinary outflow increased production of urine may provoke or aggravate complaints. These patients require careful monitoring. Patients with partial obstruction of urinary outflow, e.g. with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention and require careful monitoring.

Particularly careful monitoring is necessary in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure.
- Patients with latent or manifest diabetes. Furosemide may necessitate adjustment of control by hypoglycaemic agents in cases of diabetes mellitus
- 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).

The use of diuretics is considered to be unsafe in acute porphyria therefore caution should be exercised.

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 when compared to patients treated with risperidone alone or furosemide alone. Caution should be exercised and the risks and benefits of this combination or co-treatment should be considered prior to the decision to use. Dehydration should be avoided.

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.

This medicinal product contains approximately 3.64mg sodium per ml, less than 1mmol (23mg) sodium i.e essentially 'sodium free'

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of this preparation with non-depolarising muscle relaxants, may necessitate adjustment of the dosage of those drugs.

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.

Concurrent use of furosemide with aminoglycosides may increase the potential for ototoxicity. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

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.

Corticosteroids, carbenoxolone, liquorice, B2 sympathomimetics in large amounts, prolonged use of laxatives, reboxetine, corticotrophin and amphotericin B also cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide.

Corticosteroids administered concurrently may cause sodium retention.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Furosemide decreases the excretion of lithium salts and may cause increased serum lithium levels, 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 in patients receiving this combination.

Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis secondary to furosemide induced hyperuricaemia and ciclosporin impairment of renal urate excretion.

Patients who are at high risk of radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicylic acid and Indomethacin may reduce the effect of furosemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

In isolated cases intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of furosemide concomitantly with chloral hydrate is, therefore, not recommended.

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.

Severe diuresis may occur if metolazone is administered concomitantly.

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.

The effects of antidiabetic drugs and blood pressure increasing sympathomimetics (e.g. epinephrine, norepinephrine) may be reduced. The effects of curare-type muscle relaxants or of theophylline may be increased.

Risperidone: Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide should be considered prior to the decision to use.

4.6 Fertility, pregnancy and lactation

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.

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

Blood and lymphatic system disorders

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

Congenital, familial and genetic disorders

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

Ear and labyrinth disorders

- Tinnitus, Hearing disorders:

Gastrointestinal disorders

- Diarrhoea, nausea, vomiting.
- Acute pancreatitis

General disorders and administration site conditions

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

Hepatobiliary disorders

- Intrahepatic cholestasis, increase in liver transaminases.

Immune system disorders

- Severe anaphylactic or anaphylactoid reactions

Metabolism and nutrition disorders

- Increased excretion of sodium and chloride and consequently water
- Increased excretion of other electrolytes (in particular potassium, calcium and magnesium)

Nervous System Disorders:

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

Renal and Urinary Disorders:

- Interstitial nephritis

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

Skin and subcutaneous tissue disorders

- Itching, urticaria, other rashes or bullous lesions, erythema multiforme, bullous pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, purpura, photosensitivity.

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.

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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO3C A01

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

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 20mg in 2ml Solution for Injection should not be mixed with any other preparations.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

2ml, amber glass ampoules, glass type I, Ph.Eur. borosilicate glass, packed in cardboard cartons to contain 10x2ml 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 AUTHORISATION HOLDER

Antigen Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER

PA 73/59/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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