# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Furosemide 10 mg/ml Solution for Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml solution contains 10mg Furosemide.
Each 2ml sterile solution for injection contains 20 mg of furosemide.
Each 5ml sterile solution for injection contains 50 mg of furosemide.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

A clear and colourless solution, essentially free from visible particles.

pH of the solution is between 8.00 and 9.30.

### 4.1 Therapeutic indications

Furosemide 10 mg/ml Solution for Injection is used for the management of fluid retention and for the management of mild to moderate hypertension, either alone or as an adjunct.

### 4.2 Posology and method of administration

General: The dose used must be the lowest that is sufficient to achieve the desired effect.

Route of administration: intravenous or intramuscular

Furosemide is given intravenously only when oral administration is not feasible or is ineffective (e.g. in impaired intestinal absorption) or if a rapid effect is required. If intravenous therapy is used, it is recommended that transfer to oral therapy be carried out as soon as possible.

Intravenous furosemide must always be injected or infused slowly, a rate of 4 mg per minute must not be exceeded. The diuretic effect of Furosemide 10 mg/ml Solution for Injection is proportional to the dosage.

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 1500 mg. For information on handling and dilution please see section 6.6 Instructions for use/handling

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.

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

**4.3 Contraindications**

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 Furosemide 10 mg / ml Solution for Injection. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

**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, for example patients 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. Cautions 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.

The possibility exists of exacerbation or activation of systemic lupus erythematosus hence caution should be taken when administering frusemide to patients with a history of SLE.

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the

elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

This medicinal product contains less than 1 mmol sodium (= 23 mg) per dose, that is to say essentially 'sodium- free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of the dosage of those drugs.

The harmful effects of nephrotoxic drugs on the kidney may be increased.

Impairment of renal function may develop in patients receiving 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, corticotrophin and amphotericin B, also cause potassium loss and severe potassium depletion may occur when administered concurrently with furosemide. Carbenoxolone, liquorice in large amounts, $B_2$ sympathomimetics, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalaemia.

Corticosteroids administered concurrently may cause sodium retention.

If antihypertensive agents, diuretics or other drugs, with blood-pressure-lowering potential are given concomitantly with furosemide, a more pronounced fall in blood pressure must be anticipated.

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 ciclosporine A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide induced hyperuricaemia and cyclosporine 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.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to interrupting the administration of furosemide temporarily or at least

reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.

Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicyclic 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.

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.

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 (see section 4.4).

Levothyroxine: High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

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.

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

Fertility
The safety of furosemide during fertility has not been established.

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

Furosemide 10 mg/ml solution for injection has negligible influence on the ability to drive and use machines. Reduced mental alertness may impair ability to drive or operate dangerous machinery.

**4.8 Undesirable effects**

The frequencies are derived from literature data referring to studies where furosemide is used in a total of 1387 patients, at any dose and in any indication. When the frequency category for the same ADR was different, the highest frequency category was selected.

The following CIOMS frequency rating is used, when applicable:
Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥0.01 and <0.1%; Very rare <0.01%; Not known (cannot be estimated from available data).

**Metabolism and nutrition disorders**
Very Common: electrolyte disturbances (including symptomatic) dehydration and hypovolaemia, especially in elderly patients. Blood creatinine increased, blood triglyceride increased.
Common: hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased. Blood uric acid increased and attacks of gout, urine volume increased.
Uncommon: glucose tolerance impaired.
Not known: hypocalcemia, hypomagnesemia, blood urea increased, metabolic alkalosis, Pseudo-Bartter syndrome.

**Vascular Disorders**
Very Common: Hypotension including orthostatic hypotension.
Rare: vasculitis.
Not known: thrombosis

**Renal and urinary disorders**
Common : urine volume increased
Rare : tubulointerstitial nephritis
Not known:
- urine sodium increased, urine chloride increase, urine retention (in patients with a partial obstruction of urinary outflow, see section 4.4)
- nephrocalcinosis/nephrolithiasis in premature infants (see section 4.4)
- renal failure (see section 4.5)

**Gastrointestinal disorders**
Uncommon: nausea,
Rare: vomiting, diarrhoea.
Very Rare: pancreatitis acute

**Hepatobiliary disorders**
Very Rare: cholestasis, transaminases increased

**Ear and labyrinth disorders**
Uncommon: hearing disorders. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.
Very Rare: tinnitus.
Uncommon: deafness (sometimes irreversible)

**Skin and subcutaneous tissue disorders**
Uncommon: pruritus, urticaria, rashes, dermatitis bullous, erythema multiforme, pemphigoid, dermatitis exfoliative, purpura, photosensitivity reaction
Not known: Stevens-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).
Not Known: acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.

**Immune system disorders**
Rare: severe anaphylactic or anaphylactoid reactions.
Not known: exacerbation or activation of systemic lupus erythematosus

**Nervous system disorders**
Rare: paraesthesiae.
Common: hepatic encephalopathy in patients with hepatocellular insufficiency. (see section 4.3)
Not Known: Dizziness, fainting or loss of consciousness (caused by symptomatic hypotension or by other causes), headache.

**Blood and the lymphatic system disorders**
Common: haemoconcentration.
Uncommon: thrombocytopenia
Rare: leucopoenia, eosinophilia
Very rare: agranulocytosis, aplastic anaemia, haemolytic anaemia.

**Congenital and familiar/genetic disorders**
Not known: increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants oduring the first weeks of life.

**General disorders and administration site conditions**
Not known: following intramuscular injection, local reactions such as pain.
Rare: fever.

**Musculoskeletal and connective tissue disorders**
Not known: cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (see section 4.3)

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 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

Pharmacotherapeutic group: Diuretic, Sulfonamides, plain
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 10 mg/ml Solution for 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 Preclinical safety data

Not applicable.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium hydroxide

Sodium chloride

Hydrochloric acid

Water for Injections

## 6.2 Incompatibilities

Furosemide should not be mixed with strong acid solutions (pH lower than 5.5), such as solutions containing ascorbic acid, noradrenaline and adrenaline due to the risk of precipitation. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

Shelf life of the finished medicinal product:

2 years

After first opening: Once opened the product should be used immediately

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC protected from light only with neutral and weak alkaline solution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

2 ml or 5 ml, Type I amber glass ampoules.
Pack sizes:
10 or 25 x 2 ml ampoules or
10 or 25 x 5 ml ampoules
Not all pack sizes may be marketed

### 6.6 Special precautions for disposal and other handling

Furosemide 10 mg / ml Solution for Injection may be mixed with neutral and weak alkaline solution with pH between 7 and 10, such as 0.9% sodium chloride and Ringer's lactate solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Product containing visible particles should not be used. For single use only, discard any remaining contents after use.

Furosemide 10 mg / ml Solution for Injection should not be mixed with any other drugs in the injection bottle.

## 7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford, Norfolk IP24 3SE, United Kingdom.

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00116/0672

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2009

## 10 DATE OF REVISION OF THE TEXT

23/07/2024