

# LAVOISIER FUROSEMIDE 20 mg/2 ml, injectable solution (IM-IV)

## QUALITATIVE AND QUANTITATIVE COMPOSITION

FUROSEMIDE.....	20.00 mg
Sodium chloride .....	14.80 mg
Sodium hydroxide .....	s.q. pH 8.5 -9.5
Water for injectable preparations .....	s.q. 2.00 ml
in each 2 ml ampoule bottle	

## PHARMACEUTICAL FORM

Injectable solution (IM-IV)

## THERAPEUTIC INDICATIONS

- Hypertension associated with short-term forecasting of life-threatening visceral involvement (hypertensive emergency) particularly during:
  - ▶ hypertensive encephalopathy,
  - ▶ left ventricular depression with pulmonary oedema.
- Cardiologic emergencies: acute lung oedema, asystolic cardiac arrest.
- Severe sodium retention of cardiac, renal origin or in cirrhosis.
- X-rays of lower urinary tract and 'wash out' test with Furosemide.
- Can be used in paediatric resuscitation.

## POSOLOGY AND ADMINISTRATION

In hypertensive emergency, dose adjustment must be achieved so that fall in blood pressure does not exceed 25% of initial level within an hour after onset of injection: a too abrupt fall in blood pressure may lead to myocardic, cerebral or renal ischaemia.

### Adults

**Parenteral route:** 2 to 3 ampoules daily by slow I.V. injection:

- Injection may be repeated for the treatment of acute lung oedema if a satisfactory response does not occur.
- The switch to oral use can be achieved at any time of treatment 3 hours after an injection of Furosemide.

### Children

**IV injection:** 0.5 to 1 mg/kg daily.

## CONTRA-INDICATIONS

This drug should never be used in patients with:

- functional acute renal failure,
- hepatic encephalopathy,
- allergy to sulphamides,
- obstruction in urinary tract in patients with oliguria,
- hypovolemia or dehydration,
- lactation

In patients hemodialysed and with severe renal impairment, hepatitis with progression of the disease and severe hepatocellular insufficiency will be excluded, as in associated renal insufficiency, the major excretion path is through bile duct and accumulation may then occur.

This drug is generally not recommended for use in pregnancy and in association with lithium or sultopride (see Interactions with other drugs and other forms of interactions).

## WARNINGS AND SPECIAL PRECAUTIONS FOR USE

### Warnings

Accidental administration of furosemide may be conducive to hypovolemia associated with dehydration (see Overdose).

In patients with hepatocellular insufficiency, treatment will be administered with great caution, undertaking strict electrolyte assessments because of the potential for hepatic encephalopathy (see Special warnings and special precautions for use). Discontinuance of treatment should then be immediate.

Cerebral vascular attack, often manifested by sudden hypertension is not an indication to antihypertensor treatment in emergency. Decision must be made depending on the presence of short-term forecasting of life-threatening visceral complications.

### Special warnings and precautions for use

Each ampoule of this drug contains 7.35 mg of sodium (i.e. 3.68 mg of sodium per ml): to be taken into account in patients with strict low-salt diet.

### Electrolyte balance

#### Natremia

Natremia should be monitored prior to initiation of treatment, then at frequent intervals. Any diuretics therapy may in fact cause hyponatremia leading to complications sometimes to severe.

The decrease of natremia, initially asymptomatic, must be monitored routinely and even more often in populations at risk like elderly patients, all the more malnourished, and in cirrhotics (see Adverse Reaction and Overdose).

#### Kalaemia

The major risk of Loop diuretics is potassium depletion inducing hypokalaemia. Onset of hypokalaemia (< 3.5 mmol/l) must be prevented in certain populations at risk like elderly patients and/or malnourished and/or polymedicated, cirrhotics with oedemas and ascites, patients with coronary and cardiac insufficiency.

Hypokalaemia increases digitalis cardiac toxicity and the risk of arrhythmias.

In patients with prolonged QT interval in EKG caused by congenital or medication-related factors, hypokalaemia increases onset of severe arrhythmia, especially torsades de pointe (TdP) potentially life-threatening, especially when associated with bradycardia.

In any case, kalaemia must be more often assessed. The first assessment of plasma potassium must be performed in the week after initiation of treatment.

#### Glycemia

Mild hyperglycemic effect. However, in patients with diabetes, glycemia should be measured systematically.

#### Uricemia

Sodium depletion induced by Furosemide diminishes excretion of uric acid in urine. In patients with hyperuricemia may be more susceptible to gout attacks. Caution should be exercised in patients with gout.

### Preparation of solutions

LAVOISIER FUROSEMIDE 20 mg/2 ml injectable solutions have a pH of 9 but no buffer value. A precipitate may form if Furosemide is introduced into a solution with a pH lower than 7.

## Sportsmen

Attention should be drawn to sportsmen that this speciality contains an active ingredient likely to induce a positive reaction in the tests performed in anti-doping controls.

## Neonates and premature infants

In newborn and premature babies, high posology and prolonged treatment of Furosemide inducing a risk of renal calcification, renal echographic monitoring is recommended.

## INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS

### CONTRAINDICATED INTERACTIONS

- ◆ **Lithium:** increase of lithemia with signs of overdosage, like in low-sodium diet (diminished excretion of lithium in urine).  
If coadministration is absolutely necessary, lithemia should be strictly monitored and dose adjustment be achieved.
- ◆ **Sultopride:** increased risk of ventricular arrhythmias, especially torsades de pointe (TdP) (hypokalaemia is a predisposing factor).  
Clinical evaluation, laboratory determinations and EKG monitoring.

### Associations to be used with precaution:

- ◆ **NSAIDs (enteral route), including COX-2 selective inhibitors, acetylsalicylic acid...):** acute renal failure in patients at risk (elderly patients and/or dehydrated) with diminished glomerular filtration (inhibition of vasodilator prostaglandins due to NSAIDs).  
Hydrate the patient, control of the renal function at initiation of treatment.
- ◆ **Other hypokalemiants: amphotericine B (IV injection), gluco and mineralocorticoids (enteral route), tetracosactide, stimulant laxatives:** higher risk of hypokalaemia (additional effect).  
Kalaemia monitoring and correction, if need be: to be taken in consideration particularly with digitalis therapy. Administration of laxatives (not stimulative).
- ◆ **Digitalis:** hypokalaemia increasing digitalis toxicity. Kalaemia monitoring and possibly EKG.
- ◆ **Hyperkalemiat diuretics (amiloride, canrenoate of potassium, spironolactone, triamterene):**  
A rational combination therapy, useful in some patients should not exclude onset of hypokalaemia or, especially in patients with renal insufficiency and diabetes, of hyperkalemia.  
Kaliema monitoring, possibly EKG and, if need be, reconsider treatment strategies.
- ◆ **Aminosides (parenteral route):** increased nephrotoxic and ototoxic risks of aminosides (functional renal impairment due to dehydration by diuretics). Coadministration may be achieved with monitoring of hydration status, renal and cochleo-vestibular functions and plasma concentrations of aminoside.
- ◆ **Phenytone:** diminished diuretic effect up to 50%.  
Possibly use larger doses of diuretics.
- ◆ **Carbamazepin:** risk of symptomatic hyponatremia.  
Clinical monitoring and laboratory determinations. If possible, use another class of diuretics.
- ◆ **Angiotensin converting enzyme (ACE) inhibitors, antagonists of angiotensin II:** risk of sudden hypotension and/or acute renal insufficiency when initiating a treatment with ACE inhibitors or an inhibitor of angiotensin II, in case of preexisting sodium depletion.  
In hypertensive patients, when previous diuretic treatment may have caused sodium depletion, it is necessary:
  - either to discontinue treatment during 3 days before initiating treatment with ACE inhibitors or inhibitor of angiotensin II, and re-administer hypokalemiat diuretics if necessary.
  - or to administer reduced initial dose of ACE inhibitors or inhibitor of angiotensin II and keep up with slow progression.

In congestive cardiac insufficiency, initiate very low dose of ACE inhibitors or inhibitor of angiotensin II, possibly after reducing the dose associated with hypokalemiat diuretics.

In any case, renal function (dosage of creatinemia) must be monitored in the first weeks of treatment with ACE inhibitors or inhibitor of angiotensin II.

- ◆ **Drugs inducing torsades de pointe (TdP) (except sultopride) are: antiarrhythmics drugs of class Ia (quinidine, hydroquinidine, disopyramide), and of class III (amiodarone, sotalol, ibutilide, dofetilide), certain neuroleptics: phenothiazinic (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide), others: bepridil, cisapride, diphemanil, erythromycine IV, mizolastine, halofantrine, sparfloxacin, pentamidine, vincamine IV, moxifloxacin...**

**Higher risk of ventricular arrhythmia, especially torsades de pointe (TdP) (hypokalaemia is a predisposing factor).**

Correct any hypokalaemia prior to use and clinical evaluation, (electrolyte) assessments and EKG monitoring.

- ◆ **Metformin:** lactic acidosis caused by metformin and triggered by possible functional renal failure from diuretics especially Loop diuretics.  
Metformine should not be used when creatinemia exceeds 15 mg/l (135 µmoles/l) for men and 12 mg/l (110 µmoles/l) for women.
- ◆ **Iodine contrast products:** in case of dehydration by diuretics, increased risk of acute renal insufficiency, especially when high dose of iodized contrast products are given.  
Rehydration prior to use of iodized contrast product.
- ◆ **Baclofene:** enhanced antihypertensor effect.  
Blood pressure monitoring and dose adjustment of antihypertensors if necessary.

### Associations requiring extreme caution:

- ◆ **Corticoids, tetracosactide** (enteral route) (except hydrocortisone used as adjuvant treatment in Addison's disease): diminished antihypertensor effect (sodium retention of corticoids).
- ◆ **Neuroleptics, imipraminic antidepressants (tricyclic):** Antihypertensor effect and higher risk of orthostatic hypotension (additional effect).
- ◆ **Amifostine:** Increased antihypertensor effect.
- ◆ **Calcium (salts):** Risk of hypercalcemia with diminished excretion of calcium in urine.
- ◆ **Ciclosporine:** increased risk of creatinemia with no change in ciclosporine plasma concentrations, even with no sodium depletion.

## PREGNANCY AND LACTATION

### Use in Pregnancy

- Studies in animals have shown a teratogenic effect.
- In clinical trials, no current data are available for pertinent evaluation of possible malformative or foetotoxic effects of furosemide in pregnancy.
- Furosemide should generally be avoided in pregnancy and never be prescribed in physiological oedemas of pregnancy (requiring no treatment). Diuretics may in fact cause foetoplacental ischaemia, with risk of foetal hypotrophy.
- Diuretics (for oral administration) remain however, a key element in the treatment of oedemas resulting from cardiac, hepatic and renal insufficiency, occurring in pregnant women.

**Lactation:**

Furosemide is excreted in the maternal milk. Loop diuretics diminish lacteous secretions and lactation is inhibited from a single dose of 40 mg.

Consequently, the use of this drug should be avoided in lactation.

**ADVERSE REACTION**

Sometimes, a mild increase of uricemia (about 10 to 30 mg/l) may occur during treatment, exceptionally contributing to gout attack.

Elevated glycemia is sometimes observed, most often in intensive and short-duration treatment, especially by intravenous injection. In very rare instances, decreased tolerance to glucose was reported.

Electrolyte disturbances may be observed in relation to the action of the product: dehydration, hyperazotemia, hyponatremia, hypovolemia manifested by orthostatic hypotension and justifying discontinuance of treatment or reduced dosage. A very strict low-salt diet contributes to electrolyte imbalance.

Some hypokalaemias whether associated or not with metabolic alkalosis may be observed. They occur usually with high doses or in cirrhotics, patients malnourished and those with cardiac insufficiency (see Special warnings and precautions for use). These hypokalaemias may be very severe in patients with cardiac insufficiency and also be conducive to severe arrhythmias, especially torsades de pointe (TdP) (potentially life-threatening) principally when associated with antiarrhythmics drugs of the quinidine group.

In very rare instances, renal calcifications associated with hypercalciuria were observed in very great premature infants treated by high doses of furosemide injections for congenital cardiopathy with cardiac insufficiency.

In patients with hepatocellular insufficiency, possible onset of hepatic encephalopathy. (see Contraindications and Special warnings and precautions for use).

Allergic reactions may occasionally occur sometimes bullous reactions, lumbar pains, leucopenias and thrombopenias.

Gastrointestinal tract disturbances.

Very high doses of injectable Furosemide - (especially when recommended rates of injection (4 to 6 minutes for direct IV injection or 4 mg per minute for perfusion) have not been observed) - may induce reversible hearing impairment, and exceptional cases of irreversible impairment when associated with antibiotics of aminosides class with ototoxic effects.

**OVERDOSAGE**

Hypovolemia by dehydration with electrolyte disturbances may occur in case of overdosage. Treatment with electrolyte rebalance should then be instituted.

**CLINICAL PHARMACOLOGY****Pharmacodynamics**

LOOP DIURETICS Codes ATC: C03 CA01

**Saliuretic action:**

With the usual therapeutic doses, Furosemide has an action primarily on the upper limb of Henle's Loop, inhibiting first the reabsorption of chlorine, then of sodium. Furosemide exerts a minor action on diluting segments of the distal tubule.

Furosemide potentiates renal blood flow to the benefit of the cortical zone. This propriety is of particular interest in association with beta-blockers which may produce the reverse effect.

Furosemide does not modify glomerular filtration (this latter was shown to be higher in certain conditions). Saliuretic action raises accordingly with the doses administered and persists in patients with renal insufficiency.

**Antihypertensive action and other actions:**

Hemodynamic action is characterized by the decrease of the pulmonary capillary pressure even prior to onset of diuresis, and the increase of the capacity storage of venous vascular bed shown by plethysmography (Studies of these properties were mainly focused on IV administration).

Furosemide treats all forms of sodium retention with response proportional to dosage.

Furosemide exerts antihypertensive action, resulting both from sodium depletion and hemodynamic action.

**Pharmacokinetics**

After parenteral infusion, the major excretion path is in urine. Saliuretic action is observed within the first 5 minutes after intravenous injection.

Average elimination half-life is about one hour. This half-life is increased in premature infants.

Increased digestive elimination (biliary) in patients with renal insufficiency. There is then no accumulation of the product.

Furosemide passes into the breast milk.

**PHARMACEUTICAL DATA****Incompatibilities**

LAVOISIER FUROSEMIDE 20 mg/2 ml, injectable solution should not be mixed with other substances in the same intravenous line (a precipitate may form by acidification of the solution).

**Shelf life:** 2 years

**Storage special precautions**

Store ampoules in outer packaging, in a dark place.

**Nature and contents of container**

2 ml ampoule bottle (type I glass)

**Safety and drug handling instructions:** Discard ampoule if any brown discoloration.

**PACKAGING AND PRODUCT LICENSE NUMBER****Hospital Packaging:**

**MA 561 856-1:** 2 ml ampoule bottle (type I glass) – 100 units pack – Approved for institutions.

**CONDITIONS OF DELIVERY**

List II

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