1. NAME OF THE MEDICINAL PRODUCT
FUROSEMIDE INIBSA 20 mg/2ml SOLUTION FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of Furosemide Inibsa 20mg/2ml solution for injection contains:

- Furosemide (INN) 10.0 mg
- Excipients:
  - Sodium chloride 7.5mg

Each 2ml vial contains: 5.9 mg of sodium
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
- Oedema subsequent to cardiac or hepatic disease (ascites).
- Oedema due to kidney failure (treatment of the underlying disease takes priority in nephrotic syndrome).
- Acute heart failure, especially with pulmonary oedema (administered together with other therapeutic measures).
- Oliguria resulting from complications during pregnancy (gestosis) after compensation of blood volume.
- As a coadjuvant measure in cerebral oedema.
- Oedemas following burns.
- Hypertensive seizures, together with other hypotensive measures.
- Maintenance of forced diuresis in intoxications.

4.2. Posology and method of administration

**Posology**
Unless specifically indicated, the following dosing regimen is recommended:

**Adults and adolescents over 15 years of age:** 20 to 40 mg will be administered intravenously or intramuscularly as the starting dose.

If the diuretic effect obtained with the single dose of 20 to 40 mg of FUROSEMIDE INIBSA 20 mg/2 ml solution for injection (1 to 2 vials) is not satisfactory, the dose can be increased by 20 mg (1 vial) every two hours until the required effect is obtained. The dose found in this way is then administered once or twice a day. The maximum dose will depend on the patient's diuretic response.

The length of treatment will depend on medical criteria.

**Acute pulmonary oedema:** 40 mg FUROSEMIDE INIBSA 20 mg/2 ml solution for injection (2 vials) shall be administered as the starting dose. After 20 minutes, and if
required by the patient's condition, an additional injection of 20 to 40 mg FUROSEMIDE INIBSA 20 mg/2 ml solution for injection (1-2 vials) shall be applied.

The continuation of the treatment will depend on the diuresis and will be carried out compensating the losses of liquid and electrolytes.

In intoxications from acid or basic substances the elimination rate may increase as a result of the acidification or alkalinisation of the urine.

1 mg of furosemide per kg of body weight per day up to a maximum of 20 mg (1 vial) is calculated as a dosage regimen in intravenous or intramuscular injection. The treatment will be changed to oral treatment soon as this is possible.

**Method of administration**

When administered intravenously, FUROSEMIDE INIBSA 20 mg/2 ml solution for injection should be injected slowly, not exceeding an injection rate of 4 mg per minute (= 0.4 ml per minute).

The intravenous or intramuscular administration of FUROSEMIDE INIBSA 20 mg/2 ml solution for injection is indicated when intestinal absorption is altered or when a rapid elimination of fluids is required.

**4.3. Contraindications**

- Renal impairment with anuria.
- Hepatic coma.
- Hypokalaemia.
- Hypernatraemia and/or hypovolaemia with or without hypotension.
- Hypersensitivity to sulfonamides.

**4.4. Special warnings and precautions for use**

Except in patients with renal impairment, it is advisable to have a potassium-rich diet (meat without fat, bananas, potatoes, tomatoes, cauliflower, spinach, nuts, etc.) and even potassium salt supplements to avoid secondary hypokalaemia associated with continued use of the medicinal product.

An excessive restriction of sodium in the diet may reduce the glomerular filtration rate, and therefore the diuretic effect of the saluretics is weaker. In these cases, the diuretic action of FUROSEMIDE INIBSA 20 mg/2 ml solution for injection may increase with the intake of sodium chloride.

In prolonged treatments, creatinine and urea in blood as well as plasmatic electrolytes, particularly potassium, calcium, chloride and bicarbonate must be regularly controlled.

**Paediatric population**

Breastfed infants and children aged less than 15 years: parenteral administration must only be used in serious cases (and if used, as drop by drop infusion).

**Geriatric population**

No precautions required.

**Athletes**

Athletes are informed that this medication contains a component which could give a positive result in doping control analysis.
4.5. Interaction with other medicinal products and other forms of interaction

When cardiac glycosides are administered simultaneously, the fact that hypokalaemia increases the digitalis sensitivity of heart muscle must be taken into consideration.

In the event of simultaneous administration of glucocorticoids, the hypokalemic effect of steroids must be taken into consideration.

Furosemide may enhance the toxic effect of nephrotoxic antibiotics (e.g., aminoglycosides). As such, furosemide must be administered with care in patients with antibiotic-induced kidney damage.

It must be taken into consideration that the ototoxicity of aminoglycoside antibiotics (e.g. kanamycin, gentamicin, tobramycin) may increase with simultaneous administration of furosemide. The auditory alterations that present in such cases may be irreversible. Consequently, concomitant administration must be reserved for life-threatening indications.

Cisplatin (parenteral) and furosemide must not be co-administered due to the possible risk of ear damage.

Furosemide may weaken (e.g. antidiabetic agents and pressor amines) or enhance (e.g. salicylates, theophylline, lithium and curare-type muscle relaxants) the effects of other medicinal products.

Furosemide may enhance the action of other hypotensive medicinal products; in particular, a marked decrease in blood pressure may occur when combined with ACE inhibitors.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin) may decrease the action of furosemide, and may provoke renal impairment in the event of hypovolaemia.

4.6. Fertility, pregnancy and lactation

It must only be administered during pregnancy when strictly indicated and for a short period of time.

When furosemide must be administered to a breastfeeding mother, it should be taken into consideration that furosemide passes into human breast milk, and reduces its secretion, therefore breastfeeding must be stopped in such cases.

4.7. Effects on ability to drive and use machines

As for other drugs that modify blood pressure, patients receiving FUROSEMIDE INIBSA 20 mg/2 ml solution for injection must be warned that they must not drive or use machines if they experience dizziness or related symptoms. This is particularly important at the commencement of treatment, when the dose is increased or when alcohol is ingested concomitantly.

4.8. Undesirable effects

As is the case for other diuretics, electrolytic balance disorders may occur after prolonged administration of FUROSEMIDE INIBSA 20 mg/2 ml solution for injection.
As a result of excessive diuresis, particularly at the start of treatment and in elderly patients, circulatory disorders, which manifest as headaches, dizziness or visual disturbances may occur. In extreme cases hypovolaemia, dehydration, collapse, and blood clotting alterations may occur. Nevertheless, when the dose is adjusted individually, in general, acute haemodynamic reactions are not expected despite a rapid onset of diuresis.

Liver cirrhosis, vomiting, chronic diarrhoea due to the abuse of laxatives, and a low-potassium diet, predispose for the presentation of hypokalaemia. In these cases, adequate monitoring and replacement therapy are necessary.

A large restriction in salt intake can lead to hyponatraemia, which manifests as orthostatic hypotension, muscle cramps, anorexia, asthenia, dizziness, drowsiness, vomiting and mental confusion.

Furosemide may decrease calcaemia; signs of tetany have been observed in some cases.

It may cause nephrocalcinosis in pre-term newborns.

Allergic reactions (e.g. exanthema, interstitial nephritis) and alterations to the blood count (leukopenia, agranulocytosis, anaemia, thrombocytopenia) may occasionally appear.

Anaphylactic shock is uncommon, but if the symptoms appear it is always very serious.

In the event of hydronephrosis, prostatic hypertrophy or urethral stenosis, the administration of furosemide may worsen or cause the appearance of urinary hesitancy.

Like any other diuretic treatment, furosemide might cause a transient increase in the levels of creatinine and urea in the blood.

In susceptible patients, it should be considered that the administration of furosemide might increase the level of uric acid in the blood and trigger a gout attack.

An increase of cholesterol and triglyceride levels in blood may occur with the administration of furosemide; however, these values will normalise without suspending the treatment, in most cases, within a period of six months.

Some cases of impaired glucose tolerance have been reported, which may lead to the expression of a latent diabetes mellitus or the worsening of a pre-existing process.

Cases of acute pancreatitis, apparently caused by the administration of saluretics for several weeks, have occasionally been observed; some occurred after the administration of furosemide.

The hypoacusis which may be observed due to furosemide is uncommon, and most cases are reversible. This event can occur when furosemide is injected too quickly, particularly if kidney failure exists.

A pre-existing metabolic alkalosis (e.g. decompensated liver cirrhosis) may be aggravated upon treatment with furosemide.
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

4.9. Overdose

Signs and symptoms:
Intense diuresis with risk of dehydration and, in the event of prolonged use, hypokalaemia; excessive water and electrolyte loss may lead to delirium.

Treatment:
Fluid replacement and repeated monitoring of the electrolyte balance and metabolic constants. In the case of patients with urination disorders (prostatic hypertrophy, consciousness disorders, etc.), attempts must be made to maintain normal urine flow.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: High-ceiling diuretics; sulfonamides, plain, ATC code: C03CA01.

Furosemide is a diuretic from the sulfonamide family. Its pharmacodynamic effect is the result of an increase in sodium, chloride, potassium, calcium, magnesium, ammonium and, possibly, phosphate excretion.

Mechanism of action
The mode of action of furosemide has not been fully established and, in contrast to other sulfonamides, it does not bind to the sulfhydryl groups of renal cell proteins. Furosemide inhibits electrolyte reabsorption in both the proximal and distal tubules and in the ascending branch of the loop of Henle.

Pharmacodynamic effects
In patients with normal renal function, the response after oral or intravenous administration is similar as regards the dose.

The excessive loss of potassium, hydrogen ions and chloride may lead to a metabolic alkalosis. Urinary pH normally decreases after the administration of furosemide, although bicarbonate excretion may initially increase it temporarily. The effect of furosemide is not dependent on the patient's acid-base equilibrium.

Furosemide also has a renal vasodilatory effect, with decreased renal vascular resistance and increased local blood flow. In the congestive heart disease associated with myocardial infarction, furosemide has been shown to produce an increase in the glomerular filtration rate, as well as a decrease in peripheral vascular resistance and an increase in peripheral venous capacitance. This effect on the kidney and on peripheral circulation contributes to the production of a beneficial effect in these patients, which manifests as a decrease in the left ventricular filling pressure after the onset of diuresis.

In congestive heart disease, the administration of furosemide produces a decrease in plasma volume, an increase in haematocrit and a decrease in mean pressure, associated with an increase in cardiac efficiency and a decrease in peripheral resistance.

As is the case for other diuretics, this decrease in plasma volume has a hypotensive effect. However, the decrease in blood pressure is not pronounced.
Furosemide has less of an effect on carbohydrate metabolism and blood glucose concentration than other thiazides. However, its administration may result in an increase in blood glucose, glucosuria and glucose tolerance alterations, possibly due to hypokalaemia.

5.2. Pharmacokinetic properties

After intravenous administration, diuresis commences after 5 minutes, reaching a maximum at between 20 and 60 minutes.

Very few data are available concerning its distribution, although it crosses the placenta and passes into breast milk. Around 90% is bound to plasma proteins.

Elimination occurs in a biphasic manner. After intravenous administration of a dose of 20 to 120 mg, the elimination half-life is approximately 30 minutes. In patients with altered renal function, this half-life may be prolonged to 9.7 hours after intravenous administration of 1 g. The half-life is also longer in patients with hepatic impairment.

A small proportion of furosemide is metabolised to the defurfuryl derivative (4-chloro-5-sulfamoylanthranilic acid) in the liver. Both unchanged furosemide and its metabolite are rapidly excreted in proximal tubule by glomerular filtration and secretion.

Around 80% of the drug is eliminated in the first 24 hours. The remainder is eliminated via non-renal mechanisms, including hepatic degradation or elimination as unchanged drug in faeces.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Sodium chloride
- Sodium hydroxide (to alter the pH)
- Water for injectable preparations

6.2. Incompatibilities

FUROSEMIDE INIBSA 20 mg/2 ml solution for injection must not be mixed in the same syringe with any other medicine.

Furosemide is soluble in an alkaline medium as anthranilate. The solution for parenteral administration contains the sodium salt of the carboxylic acid without any solubilizer; it has a pH of 9 and does not have buffering action, so a pH value of less than 7 may precipitate the active ingredient. Mixtures can be stored for 24 hours at the most if the pH of the final solution is neutral or weak alkaline.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Keep in the original package to protect it from light.
6.5. Nature and contents of container and special equipment for use, administration or implantation

Topaz-coloured glass vials (Type I).

FUROSEMIDE INIBSA 20 mg/2 ml solution for injection is presented in boxes containing 5 or 100 vials of 2 ml.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or material that has been in contact with it should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. Marketing Authorisation Number(s)

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9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

31 July 1998

10. Date of Revision of the Text

July 1998