## 1. NAME OF THE MEDICINAL PRODUCT

HIBOR 2,500 IU anti Xa/0.2 ml solution for injection in pre-filled syringes.
HIBOR 3,500 IU anti Xa/0.2 ml solution for injection in pre-filled syringes.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Pharmaceutical form | Active ingredient / ml solution | Total Quantity |
|---|---|---|
| HIBOR 2,500 IU/ 0.2 ml pre-filled syringes | Bemiparin sodium (INN) 12,500 IU (anti-Xa) | 2,500 IU (anti-Xa)* |
| HIBOR 3,500 IU / 0.2 ml pre-filled syringes | Bemiparin sodium (INN) 17,500 IU (anti-Xa) | 3,500 IU (anti-Xa)* |

* Approximate anti-Factor Xa activity described in international units (IU) evaluated versus the International Low Molecular Weight Heparin Reference Standard of the WHO with amydolitic anti-Xa method with specific substrata and using the LMWHs (NIBSC) International standard.

Bemiparin sodium is derived from porcine intestinal mucous membrane.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringes.
Colourless or slightly yellowish, clear solution, free of visible particles.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of thromboembolic disease in patients (at high risk of developing VTE) undergoing total knee arthroplasty.

### 4.2 Posology and method of administration

WARNING: The different low molecular weight heparins are not necessarily equivalent. Therefore, compliance with the dosage regimen and the specific method of use for each of these medicinal products is required.

Posology

*Adults*

*Total knee arthroplastywith high risk of venous thromboembolism:*

On the day of the surgical procedure, 3,500 IU anti-Xa is to be administered by sc route, 6 hours after surgery. On subsequent days, 3,500 IU anti-Xa sc is to be administered every 24 hours.

Prophylactic treatment must be followed in accordance with the physician's opinion, during the period of risk or until the patient is completely mobilised. As a general rule, it is considered necessary to maintain prophylactic treatment for at least 7 – 10 days after the surgical procedure and until the risk of thromboembolic disease has decreased.

*Paedriatic population*

HIBOR is not recommended for use in children under 18 years due to a lack of data on safety and efficacy.

*Elderly*

No dose adjustment is required, unless renal function is altered (see section 4.2 *Posology and method of administration,* Renal impairment; 4.4 *Special warnings and precautions for use;* 5.2 *Pharmacokinetic properties).*

*Renal impairment*

(See sections 4.4 *Special warnings and precautions for use* and 5.2 *Pharmacokinetic properties).*

- For daily doses of bemiparin 3500 IU:

    - In patients with mild or moderate renal insufficiency (creatinine clearance 30-80 ml/min): no dose adjustment is necessary. However, a close monitoring is recommended.
    - In patients with severe renal insufficiency (creatinine clearance <30 ml/min) could influence the pharmacokinetics of bemiparin. Physicians should assess the individual bleeding and thrombotic risks in these patients. In some cases, the dose may be necessary to be adjusted. Based on limited pharmacokinetic data (See Section 5.2), a dose reduction up to 2,500 IU anti-Xa s.c. once daily could be recommended. A close monitoring is recommended. Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered.

*Hepatic impairment*

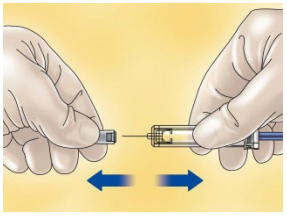
The use of bemiparin has not been studied in patients with hepatic impairment and therefore is not recommended.

Method of administration

*Subcutaneous injection technique:*

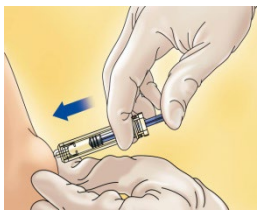
You should follow these steps:

- Wash your hands thoroughly. The patient should be sitting or lying in a comfortable position at the time of Hibor administration.
- The administration of HIBOR by subcutaneous route is performed by injecting the syringe in the subcutaneous cell tissue of the anterolateral or posterolateral abdominal waist, to 5 centimetres from the navel and any scar or bruise. Clean the skin in that area.
- Use different places for the injection on different days, for example, first on the left hand side, next time on the right.
- Pull the needle cap off the HIBOR syringe.

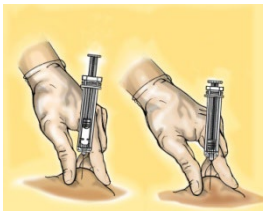


- To keep the needle sterile, make sure it doesn´t touch anything.
- The pre-filled syringe is now ready for use.

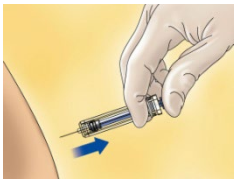
- Before injecting, do not push the plunger to get rid of any air bubbles, because you might lose the medicine.



- Hold the syringe in one hand and with your other hand, using your forefinger and thumb, gently pinch the area of skin which you've cleaned and make a skin fold.
- Insert the whole needle into the folded skin keeping the syringe as straight as possible on the body surface at a 90º angle.
- Press down on the plunger, making sure you hold the skin fold in position throughout the injection.



- Remove the syringe from the injection site keeping your finger on the plunger rod and the syringe straight. Let go of the skin fold.



- Immediately dispose the syringe throwing it into the closest sharp object´s bin (the needle pointing inside), close the container lid tightly and place it out of reach of children.


Warnings:

- Do not reuse the needle shield after injection.
- Do not rub the skin at the injection site. This will help to avoid bruises.

**4.3 Contraindications**

Hypersensitivity to sodium bemiparin, heparin or substances of porcine origin or to any of the excipients included on section 6.1.

History of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (HIT) (see section 4.4).

Active haemorrhage or increased risk of bleeding due to alterations of haemostasis.

Severe impairment of liver or pancreatic function.

Injuries or surgical interventions on the central nervous system, eyes and ears within the last 2 months.

Disseminated Intravascular Coagulation (DIC) attributable to heparin-induced thrombocytopenia.

Acute bacterial endocarditis and slow endocarditis.

Any organic lesion susceptible of bleeding (e.g.: active peptic ulcer, haemorrhagic stroke, cerebral aneurysm or cerebral neoplasms).

**4.4 Special warnings and precautions for use**

Do not administer by intramuscular route.

Due to the risk of haematoma during bemiparin administration, the intramuscular injection of other agents should be avoided.

When administering bemiparin doses of 3,500 IU the kinetics of bemiparin may be affected in patients with severe renal impairment (creatinine clearance <30 ml/min). Regular monitoring is recommended in this population. A careful assessment of the individual bleeding and thrombotic risks in these patients should be made before initiating the treatment. In mild or moderate renal impairment (creatinine clearance 30-80 ml/min) no dose adjustment seems necessary, although caution should be exercised. (See sections: 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Caution should be exercised in cases of liver failure , uncontrolled arterial hypertension, history of gastro-duodenal ulcer disease, thrombocytopenia, nephrolithiasis and/or urethrolithiasis, choroid and retinal vascular disease, or any other organic injury susceptible of bleeding, or in patients undergoing spinal or epidural anesthesia and/or lumbar puncture.

Bemiparin, like other LMWHs, can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or those taking potassium sparing drugs. The risk of hyperkalaemia appears to increase with the duration of therapy but is usually reversible (see section 4.8). Serum electrolytes should be measured in patients at risk before starting bemiparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond 7 days.

Occasionally a mild transient thrombocytopenia (HIT type I) at the beginning of therapy with heparin with platelet counts between 100,000/mm3 and 150,000/mm3 due to temporary platelet activation has been observed (see section 4.8). As a general rule, no complications occur, therefore treatment can be continued.

In rare cases antibody-mediated severe thrombocytopenia (HIT type II) with platelet counts clearly below 100,000/mm3 has been observed (see section 4.8). This effect usually occurs within 5 to 21 days after the beginning of treatment, although in patients with a history of heparin-induced thrombocytopenia this may occur sooner.

Therefore, platelet counts are recommended before administration of bemiparin, on the first day of therapy and then regularly 3 to 4 days and at the end of therapy with bemiparin. In practice, treatment must be discontinued immediately and an alternative therapy initiated if a significantly reduced platelet count is observed (30 to 50 %), associated with positive or unknown results of in-vitro tests for anti-platelet antibody in the presence of bemiparin, other LMWHs and /or heparins.

As with other heparins, cases of cutaneous necrosis, sometimes preceded by purpura or painful erythematous blotches have been reported with bemiparin (see section 4.8). In such cases, treatment should be discontinued immediately.

In patients undergoing epidural or spinal anesthesia or lumbar puncture, the prophylactic use of heparin may very rarely be associated with epidural or spinal haematoma, resulting in prolonged or permanent paralysis (see section 4.8). The risk is increased by the use of an epidural or spinal catheter for anesthesia, by the concomitant use of drugs affecting haemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants (see section 4.5), and by traumatic or repeated puncture.

When reaching a decision as to the interval between the last heparin administration at prophylactic doses and the placement or removal of an epidural or spinal catheter, the product characteristics and the patient profile should be taken into account. The subsequent dose of bemiparin should not take place until at least four hours after removal of the catheter. The subsequent dose should be delayed until the surgical procedure is completed.

Should a physician decide to administer anticoagulation treatment in the context of epidural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment, such as back pain, sensory and motor deficits (numbness and weakness in lower limbs) and bowel or bladder dysfunction. Nurses should be trained to detect such signs and symptoms. Patients should be instructed to inform a nurse or a clinician immediately if they experience any of the above symptoms.

If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

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

Bemiparin interactions with other medicinal products have not been investigated and the information given on this section is derived from data available from other LMWHs.

The concomitant administration of bemiparin along with the following medicinal products is not advisable:

Vitamin K antagonists and other anticoagulants, acetyl salicylic acid, other salicylates and NSAIDs, ticlopidine, clopidogrel, other platelet inhibitors systemic glucocorticoids and dextran.

All these drugs increase the pharmacological effect of bemiparin since they interfere with its action on coagulation and/or platelet function, with the subsequent increase of the risk of bleeding. If the combination cannot be avoided, it should be used with careful clinical and laboratory monitoring.

Medicinal products that increase the serum potassium concentration should only be taken concomitantly under special careful medical supervision.

Interaction of heparin with intravenous nitroglycerine (which can result in a decrease in efficacy) cannot be ruled out for bemiparin.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Animal studies have not shown any evidence of teratogenic effects with the use of bemiparin (see section 5.3). For bemiparin, clinical data on exposed pregnancies are limited. However, caution should be exercised when prescribing to pregnant women.

It is unknown whether bemiparin crosses placental barrier.

Breastfeeding

There is not sufficient information available as to whether bemiparin passes into breast milk. Therefore, when it is necessary for lactating mothers to receive HIBOR, they will be advised to avoid breast-feeding.

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

HIBOR has no or negligible influence on the ability to drive and use machines **4.8 Adverse reactions**
The most commonly reported adverse reaction is haematoma and/or ecchymosis at the injection site, occurring in approximately 15% of patients receiving HIBOR.

Osteoporosis has been associated with long-term heparin treatment.

The adverse reactions are listed by system organ class and frequency:

- very common (≥1/10)
- common (≥1/100 to <1/10)
- uncommon (≥1/1,000 to <1/100)
- rare (≥1/10,000 to <1/1,000)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data).

The frequency of adverse events (AEs) reported with bemiparin is similar to those reported with other LMWHs and it as it follows:

| **System organ classification** | **Very common (≥ 1/10)** | **Common (≥1/100 a <1/10)** | **Uncommon (≥1/1.000 a <1/100)** | **Rare (≥1/10.000 a <1/1.000)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract) | Mild and transient trombocytopenia (HIT type I) (see section 4.4) | Severe thrombocytopenia (type II) (see section 4.4) | |
| Immune system disorders | | | Cutaneous allergic reactions (urticaria, pruritus) | Anaphylactic reactions (nausea, vomiting, fever, dyspnea, bronchospasm, glottis oedema, hypotension, urticaria, pruritus) | |
| Metabolism and nutrition disorders: | | | | | Hyperkalemia (see section 4.4) |
| Hepatobiliary disorders: | | Mild and transient elevations of the transaminase levels (AST, Alanine aminotransferase ALT) and gamma-glutamil | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | transpeptidase (GGT) | | | |
| Skin and subcutaneous tissue disorders | | | | Cutaneous necrosis at the injection site (see section 4.4). | |
| General disorders and alterations at the administration site | Ecchymosis at injection site.<br>Haematoma and pain at injection site | | | Epidural and spinal haematomas following epidural or spinal anesthesia and lumbar puncture. These haematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see section 4.4) | |

**4.9 Overdose**

Bleeding is the main symptom of overdosage. If bleeding occurs, bemiparin treatment should be discontinued depending on the severity of the haemorrhage and the risk of thrombosis.

Minor haemorrhages rarely need specific treatment. In case of major haemorrhages, the administration of protamine sulphate may be needed.

The neutralisation of bemiparin with protamine sulphate has been studied in *in-vitro* and *in-vivo* systems, with the aim of observing the reduction of anti-Xa activity and the effect on the Activated Partial Thromboplastin Time (APTT). Protamine sulphate exerts a partial decrease on anti-Xa activity during 2 hours after its intravenous administration, at a dose of 1.4 mg of protamine sulphate each 100 IU anti-Xa administered.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agent, heparin group. ATC code: B01AB12.

Bemiparin sodium is a LMWH obtained by depolymerization of heparin sodium from porcine intestinal mucous. Its mean molecular weight (MW) is approximately 3,600 Daltons. The percentage of chains with MW lower than 2,000 Daltons is less than 35%. The percentage of chains with MW from 2,000 to 6,000 Daltons ranges between 50-75%. The percentage of chains with MW higher than 6,000 Daltons is less than 15%.

The anti-Xa activity ranges between 80 and 120 anti-Xa IU per mg and the anti-IIa activity ranges between 5 and 20 anti-IIa IU per mg, calculated in relation to dry matter. The anti-Xa/anti-IIa ratio is approximately 8.

In animal experiment models, bemiparin has shown antithrombotic activity and a moderate haemorrhagic effect.

In humans, bemiparin has confirmed its antithrombotic activity and, at the recommended doses, it does not significantly prolong global clotting tests.

**5.2 Pharmacokinetic properties**

The pharmacokinetic properties of bemiparin have been studied by the evolution of the plasmatic anti-Xa activity. The determination is performed using the amydolitic method; it is based on the W.H.O. First International Low Molecular Weight Heparin Reference Standard (National Institute for Biological Standards and Control, NIBSC).

The absorption and elimination processes follow a linear kinetic of 1st order.

Absorption

Bemiparin sodium is rapidly absorbed following subcutaneous injection and the bioavailability is estimated to be 96%. The maximum anti-Xa effect at prophylactic doses of 2,500 IU and 3,500 IU occurs 2 to 3 hours after subcutaneous injection of bemiparin, reaching peak activities of 0.34 ± (0.08) and 0.45 ± (0.07) IU anti-Xa/ml, respectively. Any anti-IIa activity was detected at these doses. The maximum anti-Xa effect at treatment doses of 5,000 IU, 7,500 IU, 10,000 IU and 12,500 IU occurred 3 to 4 hours after subcutaneous injection of bemiparin, reaching peak activities of 0.54 ± (0.06), 1.22 ± (0.27), 1.42 ± (0.19) and 2.03 ± (0.25) IU anti-Xa/ml, respectively. An anti-IIa activity of 0.01 IU/ml was detected at doses of 7,500 IU, 10,000 IU and 12,500 IU.

Elimination

Bemiparin in the dose range of 2,500 IU to 12,500 IU has an approximate half-life of 5 to 6 hours, and should therefore be administered once daily.

There are currently no data available with regards to plasma protein binding, metabolism and excretion of bemiparin in humans.

Elderly: the results of a pharmacokinetic analysis of a clinical study carried out in young healthy volunteers and elderly (≥65 years) showed no significant differences on the kinetic profile of bemiparin between young and old when the renal function is normal.

Renal impairment: (see sections: 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use) the results from a pharmacokinetic analysis of the clinical trial conducted in young, elderly and subjects with varying degrees of renal impairment (creatinine clearance <80 ml/min), administering multiple prophylactic doses (3,500 IU/24 h) and a single therapeutic dose (115 IU/kg) of bemiparin, showed a correlation between creatinine clearance and most pharmacokinetic parameters of anti-Xa activity. In addition, it was shown that exposure to bemiparin (based on AUC of anti-Xa activity) was significantly higher in the group of volunteers with severe renal impairment (creatinine clearance <30 ml/min) compared to the rest of groups of volunteers.

On the other hand, pharmacokinetic simulations were conducted to evaluate the profile of bemiparin after administration of ten consecutive daily doses. The mean maximum anti-Xa activity (Amax) simulated after 10 prophylactic doses (3,500 IU/24 h) was in all groups between 0.35 and 0.60 IU anti-Xa/ml; however, in the group of severe renal impairment (creatinine clearance <30 ml/min) one subject showed a value of

Amax=0.81 IU anti-Xa/ml after the tenth dose. Simulating a dose reduction up to 2,500 IU/24 h, the model predicted values of Amax lower than 0.60 IU anti-Xa/ml (mean value of Amax= 0.42 IU anti-Xa/ml) for all volunteers from the group of severe renal impairment. In addition, the predicted mean of Amax after 10 therapeutic doses (115 IU/kg/24 h) was between 0.89 and 1.22 IU anti-Xa/ml in all groups; also, a volunteer from the severe renal impairment group showed a value of Amax=2.09 IU anti-Xa/ml after the last administration. When it was simulated a dose adjustment up to 75% of the therapeutic dose (86.25 IU/kg/24 h) it was predicted an Amax of 1.60 IU anti-Xa/ml for the aforementioned volunteer, and at the same time the mean Amax (0.91 IU anti-Xa/ml) of the severe renal impairment group remained within the range observed for the rest of the groups without dose adjustment.

### 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 and toxicity to reproduction.

Acute and repeated dose toxicity studies following subcutaneous administration of bemiparin in animals have revealed alterations consisting essentially in reversible, dose-dependent haemorrhagic lesions at the injection site. These were considered to result from exaggerated pharmacological activity.

In the studies of reproductive toxicity performed with bemiparin in pregnant rats and rabbits, between days 6 and 18 of the pregnancy, no mortality was recorded among the females treated with bemiparin. The main clinical signs recorded were subcutaneous haematomas that were attributable to a pharmacological effect of the test item. No treatment-related embryotoxic effect external, skeletal and/or visceral alterations were recorded in the examination of fetuses.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

2 years.

After first opening, HIBOR should be used immediately.

### 6.4 Special precautions for storage

Do not store above 25ºC. Do not freeze.

### 6.5 Nature and contents of container

Disposable prefilled syringes (glass type I) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel) charged with 0.2 ml of solution for injection. Packs of 2 syringes.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Single-use container. Discard any unused content. Do not use if the protective package is opened or damaged. Only clear colourless or slightly yellowish solutions, free of visible particles, should be used.

Any unused product or waste material should be disposed in accordance with local requirements.

**7. MANUFACTURER**

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Julian Camarillo, 35, Madrid,
28037 Spain

**8. DATE OF REVISION OF THE TEXT**

March 2022