BEMIPARIN SODIUM

HIBOR®

2500 IU anti-Factor Xa / 0.2 mL Solution for Injection
3500 IU anti-Factor Xa / 0.2 mL Solution for Injection
5000 IU anti-Factor Xa / 0.2 mL Solution for Injection
7500 IU anti-Factor Xa / 0.3 mL Solution for Injection
10000 IU anti-Factor Xa / 0.4 mL Solution for Injetion

Solution for Injection (SC) Antithrombotic Agent

FORMULATION:

- **Each 0.2 mL solution contains:**
  Bemiparin sodium. 2500 IU anti-Factor Xa
- **Each 0.2 mL solution contains:**
  Bemiparin sodium. 3500 IU anti-Factor Xa
- **Each 0.2 mL solution contains:**
  Bemiparin sodium. 5000 IU anti-Factor Xa
- **Each 0.3 mL solution contains:**
  Bemiparin sodium. 7500 IU anti-Factor Xa
- **Each 0.4 mL solution contains:**
  Bemiparin sodium. 10000 IU anti-Factor Xa

*Potency is described in International anti-Factor Xa activity units (IU) of the 1st International Low Molecular Weight Heparin (LMWH) Reference Standard.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties:
Bemiparin sodium is a LMWH obtained by depolymerization of heparin sodium from porcine intestinal mucosa. 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 80-120 anti-Xa IU per mg and the anti-IIa activity ranges between 5 and 20 anti-IIa IU per calculated in relation to dry matter. The anti-Xa/anti-IIa ratio is 8. In animal experiment models, bemiparin has shown antithrombotic activity and moderate hemorrhagic effect. In humans, bemiparin has confirmed its antithrombotic activity and, at the recommendedoses, it does not significantly prolong global clotting tests.

Pharmacokinetic properties:
The pharmacokinetic properties of bemiparin have been determined by measuring the plasma anti-Xa activity using the amydolitic method established by WHO as the 1st International Standard for LMW heparin. The absorption and elimination processes follow a linear kinetic of the first order.

Absorption:
Bemiparin sodium is rapidly absorbed following subcutaneous injection and the bioavailability is estimated to be 96%.The maximum plasma anti-Xa effect at prophylactic doses of 2500 IU and 3500 IU occurs 2 to 3 hours after SC injection of bemiparin, reaching peak activities in the order of 0.34 ± 0.08 and 0.45 ± 0.07 IU anti-Xa/mL, respectively. Anti-IIa activity was not detected at these doses. The maximum plasma anti-Xa effect at treatment doses of 5000 IU, 7500 IU, 10000 IU and 12500 IU occurs 3 to 4 hours after SC injection of bemiparin, reaching peak activities in the order of 0.54 ± 0.06, 1.22 ± 0.27, 1.42 ± 0.19 and 2.03 ± 0.25 IU anti-Xa/mL, respectively. Anti-IIa activity of 0.01 IU/ mL was detected at doses of 7500 IU, 10000 IU and 12500 IU.

Elimination:
Bemiparin administered in the dose range of 2500 IU to 12500 IU has an approximate half-life of 5-6 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.

CONTRAINDICATIONS:

- Hypersensitivity to bemiparin sodium, heparin or substances derived from pigs.
- History of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia (HIT) (see: Special warnings & precautions for use).
- Active hemorrhage or increased risk of bleeding due to impairment of haemostatic.
- Severe impairment of liver and pancreas function.
- Injuries & operations on the central nervous system, eyes and ears.
- Disseminated Intravascular Coagulation (DIC) attributable to heparin-induced thrombocytopenia.
- Acute bacterial endocarditis and slow endocarditis.
- Organic lesion with high risk of bleeding (e.g. active peptic ulcer, hemorrhagic stroke, cerebral aneurysm or cerebral neoplasms.
- In patients receiving heparin for treatment rather than prophylaxis, locoregional anesthesia in elective surgical procedures is

WARNING AND PRECAUTIONS

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.

Special warnings and precautions for use:

- Do not administer by the IM route.
- Should not be mixed with any other injections or infusions.
- Due to the risk of hematoma during bemiparin administration, the IM injection of other agents should be avoided.
- Caution should be exercised in patients with liver and renal failure, uncontrolled arterial hypertension, history of gastro-duodenal ulcer disease, thrombocytopenia, nephrolithiasis and/or urethrolithiasis choroids and retinal vascular disease, or any other organic lesion with an increased risk of bleeding complications, or in patients undergoing spinal or epidural anesthesia and/or lumbar puncture.

Bemiparin, like other LMWHs, can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium or taking potassium-sparing drugs. The risk of hyperkalemia appears to increase with the duration of therapy but is usually reversible. Serum electrolytes should be measured in patients at risk before starting bemiparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days. Occasionally a mild transient thrombocytopenia (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: Adverse effects). As a rule no complica-tions occur, therefore treatment can be continued. In rare cases, antibody mediated severe thrombocytopenia (type II) with platelet counts clearly below 100,000/mm3 has been observed (see: Adverse effects). This effect usually occurs within 5 to 21 days after the beginning of treatment in platelets with a history of heparin-induced thrombocytopenia this may occur sooner.

Platelet counts are recommended before administration of bemiparin, on the first day of therapy and then regularly every 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 or other LMWHs and /or heparins. As with other heparins, cases of cutaneous necrosis, sometimes preceded by purpura or painful erythematosus blotches have been reported with bemiparin (see Adverse effects). 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 hematoma, resulting in prolonged or permanent paralysis (see: Adverse effects). The risk is increased by the use of epidural or spinal catheter for anesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants (see: Drug Interaction) 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. At least 12 hours should elapse for LMWH. 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.
Patient receiving treatment doses of bemiparin wilrequire delays of at least 24 hours to assure normal haemostasis at the time of needle insertion. Should a physician decide to administer anticoagulation treatment in the context of epidural or spinal anesthesia, 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 these symptoms. If signs or symptoms of epidural or spinal hematoma are suspected, urgent diagnosis and treatment including spinal decompression should be initiated.

INDICATIONS:
For the treatment of established deep vein thrombosis with or without pulmonary embolism.

DOSAGE AND METHOD OF ADMINISTRATION:
Method of administration:
Subcutaneous injection technique.
The pre-filled syringes are ready for immediate use and must not be purged before the SC injection. The injection should be given in the subcutaneous cell tissue of the anterolateral or posterolateral abdominal waist, alternately on the left and right sides. The needle should be fully inserted, perpendicularly and not tangentially, into the thick part of a skin fold held between the thumb and the forefinger. The skin fold should be held throughout the whole injection. Do not rub the injection site

Adults: Surgical

General surgery with moderate risk of venous thromboembolism:
On the day of the surgical procedure, 2500 IU anti-Xa is to be administered by SC route, 2 hours before or 6 hours after surgery. On subsequent days, 2500 IU anti-Xa SC are to be administered every 24 hours.

Orthopedic surgery with high risk of venous thromboembolism:
On the day of the surgical procedure, 3500 IU anti-Xa is to be administered by SC route, 2 hours before or 6 hours after surgery. On subsequent days, 3500 IU anti-Xa are to be administered every 24 hours. As a general rule, it is considered necessary to maintain prophylactic treatment for at least 7 to 10 days after the surgical procedure and until the risk of thromboembolic diseases has decreased.

Non-surgical

Non-surgical patients with moderate to high risk of venous thromboembolism:
The recommended dose of bemiparin is 2500 IU/day or 3500 IU/day by SC route, according to whether the set of risk factors of the patients defines them as mild or high-risk thromboembolic patients. Treatment must be continued, according to the physician's criteria, during the risk period or until the complete mobilization of the patient.

In recurrent venous thromboembolism in patients with deep vein thrombosis and transient risk:
BEMIPARIN SODIUM (HIBOR) can be administered at a fixed dose of 3500 IU/day (3 months) in patients who have received appropri-ate initial anticoagulant treatment for deep vein thrombosis with or without pulmonary embolism, as therapeutic alternative to the administration of oral anticoagulants or whenever they are contraindicated.

In extracorporeal circuit during hemodialysis:
For patients undergoing repeated hemodialysis of no longer than 4 hours in duration and with no risk of bleeding, the prevention of clotting in the extracorporeal circuit during hemodialysis is obtained by injecting a single dose in the form of bolus into the arterial line at the beginning of the dialysis session. For patients weighing less than 60 kg, the dose will be 2500 IU, whereas for patients weighing more than 60 kg, the dose will be 3500 IU.

Treatment of deep vein thrombosis:
BEMIPARIN SODIUM (HIBOR) should be administered by the SC at a dose of 115 IU anti-Xa/kg weight, once daily. The recommended duration of treatment is 5 to 9 days. The daily dose generally corresponds depending on the bodyweight range to the following doses and volumes of the product in prefilled syringes: < 50 kg, 0.2 mL (5000 IU anti-Xa); 50-70 kg, 0.3 mL (7500 IU anti-Xa); > 70 kg, 0.4 mL (10000 IU anti-Xa). In patients weighing more than 100 kg bodyweight, the dose should be calculated on the basis of 115 IU anti-Xa/kg/day, where the concentration of anti-Xa is 25,000 IU/mL. In the absence of any contraindication, oral anticoagulation should be commenced 3-5 days after beginning BEMIPARIN SODIUM (HIBOR) first administration, and the dose adjusted so as to keep the International Normalized Ratio (INR) value between 2-3 times the control value. Bemiparin administration can be stopped as soon as the said INR value is achieved. Oral anticoagulation should be continued for at least 3 months.

Children:
The safety and efficacy of the use of bemiparin in children has not been established, therefore the usage in children is not recommended.

Elderly:
No dose adjustment required.

Renal and hepatic impairment:
There are insufficient data to recommend a dose adjustment of bemiparin in this group of patients.

DRUG INTERACTION:
- Bemiparin interactions with other medicinal products have not been investigated and the information given on the section is dfrom data available from other LMWH.
- The concomitant administration of bemiparin with Vit. K antagonists and other anticoagulants, acetyl salicylic acid and otherand NSAIDs ticlopidine, clopidogrel and other platelet inhibitors, systemic glucocorticoids and dextran is not advisable.
- All these drugs increase the pharmacological effect of bemiparin by interfering with its action on coagulation and/or plateleand increasing the risk of bleeding.
- If the combination cannot be avoided, it should be used with careful clinical and laboratory monitoring.
- Preparations known to increase the serum potassium concentration should only be taken concomitantly under careful medical supervision.
- Interaction of heparin with intravenous nitroglycerine (which can result in a decrease in efficacy) cannot be ruled out for bemiparin.

PREGNANCY AND LACTATION:
Pregnancy: No reproductive toxicity studies have been performed with bemiparin. Animal studies have not shown any evidence of teratogenic effects with the use of LMWHs. There are no data to evaluate the possible teratogenic or fetotoxic effect of bemiparin in pregnant women so the potential risk for humans is unknown. It is also unknown whether bemiparin crosses the placental barrier. Therefore, it is not recommended for use in pregnancy unless clearly necessary.
Lactation: Insufficient information is available as to whether bemiparin passes into breast milk. Therefore, where it is necessary for lactating mothers to receive BEMIPARIN SODIUM (HIBOR) they should be advised to avoid breastfeeding.

ADVERSE EFFECTS:
The most commonly reported adverse reaction is hematoma and/or ecchymosis at the injection site occurring in approximately 15% of patients receiving BEMIPARIN SODIUM (HIBOR). Osteoporosis has been associated with long-term heparin treatment. The frequency of AEs reported with Bemiparin are similar to those reported with other LMWHs and is as follows:
Very common (≥ 1/10):
- Ecchymosis at injection site
- Common (≥ 1/100 < 1/100):
- Haematoma and pain at injection site.
- Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract).
- Mild and transient elevations of transaminases (ASAT, ALAT) and gamma-GT levels.

Uncommon (≥ 1/1000 < 1/100):
- Cutaneous allergic reactions (urticaria, pruritus).
- Mild and transient thrombocytopenia (type I) (see: Special warnings and precautions for use).

Rare (< 1/1000):
- Anaphylactic reactions (nausea, vomiting, fever, dyspnoea, bronchospasm, glottis edema, hypotension, urticaria, pruritus).
- Severe thrombocytopenia (type ll) (see: Special warnings and precautions for use).
- Cutaneous necrosis at the injection site (see: Special warnings and precautions for use).

Epidural and spinal hematoma following epidural or spinal anesthesia and lumbar puncture. These hematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see: Special warnings and precautions for use).

OVERDOSE AND TREATMENT:
Bleeding is the main symptom of overdose. Bemiparin should be discontinued depending on the severity of the hemorrhage and the risk of thrombosis. Minor hemorrhages rarely need specific treatment. In case of major hemorrhages, administration of protamine sulphate may be needed. The neutralization of bemiparin with protamine sulphate has been studied *in-vitro* and *in-vivo*, with the aim of observing the reduction of anti-Xa activity and the effect on the APTT. Protamine sulphate exerts a partial decrease on anti-Xa activity for 2 hours after its intravenous administration, at a dose of 1.4 mg of protamine sulphate each 100 IU anti-Xa administered.

STORAGE CONDITION:
Store at temperatures not exceeding 30ºC.For subcutaneous use.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction report to the FDA:
www.fda.gov.ph

AVAILABILITY:
- Bemiparin sodium 2500 IU anti-Factor Xa / 0.2 mL Solution for Injection:In a box of 2 plastic trays containing 0.2 mL solution in 0.5 mL pre-filled syringe (Type I glass) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel).

- Bemiparin sodium 3500 IU anti-Factor Xa / 0.2 mL Solution for Injection:In a box of 2 plastic trays containing 0.2 mL solution in 0.5 mL pre-filled syringe (Type I glass) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel).
- Bemiparin sodium 5000 IU anti-Factor Xa / 0.2 mL Solution for Injection:In a box of 2 plastic trays containing 0.2 mL solution in 0.5 mL pre-filled syringe (Type I glass) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel).
- Bemiparin sodium 7500 IU anti-Factor Xa / 0.3 mL Solution for Injection:In a box of 2 plastic trays containing 0.3 mL solution in 0.5 mL pre-filled rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel).

- Bemiparin sodium 10000 IU anti-Factor Xa / 0.4 mL Solution for Injection:In a box of 2 plastic trays containing 0.4 mL solution in 0.5 mL pre-filled syringe (Type I glass) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel).

Bemiparin sodium (Hibor) 2500 IU : BRP - 008
Bemiparin sodium (Hibor) 3500 IU : BRP - 009
Bemiparin sodium (Hibor) 5000 IU : BRP - 010
Bemiparin sodium (Hibor) 7500 IU : BRP - 011
Bemiparin sodium (Hibor) 10000 IU : BRP - 012

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