Core Safety Profile

Active substance: Bemiparin
Pharmaceutical form(s)/strength: Solution for injection in pre-filled syringes, 25,000 IU per ml
P-RMS: ES/H/PSUR/0020/001
Date of FAR: 12.01.2011
4.2 Posology and method of administration

WARNING: The different low molecular weight heparins are different and are not necessarily equivalent. Therefore it is important to comply with the dosage regimen and the specific method of use specified for each of these medicinal products.

Adults

Treatment of deep vein thrombosis

Bemiparin 25,000 IU should be administered by the subcutaneous route at a dose of 115 IU anti-Xa/kg weight, once daily. The recommended duration of treatment is 7 ± 2 days. The daily dose generally corresponds - depending on the body weight range - to the following doses and volumes of the product in prefilled syringes: < 50 kg, 0.2 ml (5,000 IU anti-Xa); 50-70 kg, 0.3 ml (7,500 IU anti-Xa), ≥ 70 kg, 0.4 ml (10,000 IU anti-Xa). In patients weighing more than 100 kg body-weight, 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 25,000 IU 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

Bemiparin is not recommended for use in children due to a lack of data on safety and efficacy.

Elderly

No dose adjustment required.

Renal and hepatic impairment

There are insufficient data to recommend dose adjustment of bemiparin in this group of patients.

Method of administration. Subcutaneous injection technique

The pre-filled syringes are ready for immediate use and must not be purged before the subcutaneous injection. When bemiparin is administered subcutaneously, 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.

4.3 Contraindications

Hypersensitivity to bemiparin sodium, heparin or substances of porcine origin.

History of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (HIT) (see section 4.4).
Active haemorrhage or increased risk of bleeding due to impairment of haemostasis.
Severe impairment of liver or pancreatic function.
Injuries to or operations 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 endocarditis lenta.
Any organic lesion with high risk of bleeding (e.g.: active peptic ulcer, haemorrhagic stroke, cerebral aneurysm or cerebral neoplasms).
In patients receiving heparin for treatment rather than for prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated.

4.4 Special warnings and precautions for use

Do not administer by the intramuscular route.
Due to the risk of haematoma during bemiparin administration, the intramuscular injection of other agents should be avoided.
Caution should be exercised in patients with liver or renal failure (anti-factor Xa levels should be regularly monitored in patients with severe renal impairment), uncontrolled arterial hypertension, history of gastro-duodenal ulcer disease, thrombocytopenia, nephrolithiasis and/or urethrolithiasis, choroid and retinal vascular disease, or any other organic lesion with an increased risk of bleeding complications, or in patients undergoing spinal or epidural anaesthesia 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/mm$^3$ and 150,000/mm$^3$ 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/mm$^3$ 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.

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 anaesthesia or lumbar puncture, the prophylactic use of heparin may very rarely be associated with epidural or spinal haematomas, resulting in
prolonged or permanent paralysis (see section 4.8). The risk is increased by the use of an epidural or spinal catheter for anaesthesia, 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 and the following medicinal products is not advisable:

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

All these drugs increase the pharmacological effect of bemiparin by interfering with its action on coagulation and/or platelet function and increasing 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 especially 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 Pregnancy and lactation

Pregnancy

Animal studies have not shown any evidence of teratogenic effects with the use of bemiparin. For bemiparin, no clinical data on exposed pregnancies are available. Therefore, caution should be exercised when prescribing to pregnant women. It is unknown whether bemiparin crosses placental barrier.

Lactation
Insufficient information is available as to whether bemiparin passes into breast milk. Therefore, where it is necessary for lactating mothers to receive bemiparin, they should be advised to avoid breast-feeding.

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

Bemiparin has no influence on the ability to drive and use machines.

### 4.8 Undesirable effects

The most commonly reported adverse reaction is haematoma and/or ecchymosis at the injection site, occurring in approximately 15% of patients receiving bemiparin.

Osteoporosis has been associated with long-term heparin treatment.

The undesirable effects 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) and 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 is as follows:

<table>
<thead>
<tr>
<th>System organ class and frequency</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic systems disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Mild and transient thrombocytopenia (HIT type I) (see section 4.4)</td>
</tr>
<tr>
<td>Rare</td>
<td>Severe thrombocytopenia (type II) (see section 4.4)</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cutaneous allergic reactions (urticaria, pruritus)</td>
</tr>
<tr>
<td>Rare</td>
<td>Anaphylactic reactions (nausea, vomiting, fever, dyspnea, bronchospasm, glottis oedema, hypotension, urticaria, pruritus)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>Hyperkalemia (see section 4.4)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Mild and transient elevations of transaminases (ASAT, ALAT) and gamma-GT levels.</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Cutaneous necrosis at the injection site (see section 4.4).</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions:</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Ecchymosis at injection site.</td>
</tr>
</tbody>
</table>
Rare

Haematoma and pain at injection site.

Epidural and spinal haematomas following epidural or spinal anaesthesia 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 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, administration of protamine sulphate may be needed.

The neutralisation of bemiparin with protamine sulphate has been studied 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 for 2 hours after its intravenous administration, at a dose of 1.4 mg of protamine sulphate each 100 IU anti-Xa administered.