Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bemiparin sodium: 2500 IU (anti Factor Xa*) per 0.2 ml pre-filled syringe (equivalent to 12500 IU (antiFactor Xa*) per millilitre solution for injection).
Potency is described in International anti-Factor Xa activity units (IU) of the 1st International Low Molecular Weight Heparin Reference Standard.
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 undergoing general surgery.

Prevention of clotting in the extracorporeal circuit during haemodialysis.

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

General surgery with moderate risk of venous thromboembolism:

On the day of the surgical procedure, 2,500 IU anti-Xa is to be administered by subcutaneous route (sc), 2 hours before or 6 hours after surgery. On subsequent days, 2,500 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 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.

Prevention of clotting in the extracorporeal circuit during haemodialysis:

For patients undergoing repeated haemodialysis of no longer than 4 hours in duration and with no risk of bleeding, the prevention of clotting in the extracorporeal circuit during haemodialysis 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 2,500 IU, whereas for patients weighing more than 60 kg, the dose will be 3,500 IU.

Paediatric population

The safety and efficacy of Zibor in children has not been established due to a lack of data.

Older people

No dose adjustment required, if the renal function is impaired please 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 section: 4.4 Special warnings and precautions for use; 5.2 Pharmacokinetic properties)

Prevention of thromboembolic disease in patients undergoing general surgery.

- In patients with renal insufficiency (creatinine clearance <80 ml/min): limited available data suggests that no dose adjustment is necessary (See Section 5.2). A close monitoring is recommended. Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered in patients with severe renal insufficiency (creatinine clearance <30 ml/min).

Hepatic impairment

There are insufficient data to recommend a 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 Zibor 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.

In some package sizes, the prefilled syringe may be combined to a safety device system.

For syringes with safety device system the needle must be oriented away from the user and anyone else who is present. The safety system is activated by pressing firmly on the plunger rod. The protective sleeve will automatically cover the needle and will produce an audible click which confirms the activation of the device.

Immediately, the syringe must be discarded by throwing it into the nearest sharps bin (the needle in). The container lid must be closed tightly and the container placed out of the reach of children.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
Hypersensitivity to heparin or its derivatives, including other low molecular weight heparins, 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 slow endocarditis.
Any organic lesion with high risk 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 the intramuscular route.
Due to the risk of haematoma during bemiparin administration, the intramuscular injection of other agents should be avoided.

When using daily doses of bemiparin 2,500 IU in patients with renal impairment (creatinine clearance <80 ml/min) no dose adjustment seems necessary, although caution should be exercised due to the limited data. However, it should be taken into

account that the kinetics of bemiparin may be affected in patients with severe renal impairment (creatinine clearance <30 ml/min). (See Sections 4.2 and 5.2). Regular monitoring is recommended in this population.

Caution should be exercised in patients with 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 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/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.

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 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 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
Insufficient information is available as to whether bemiparin passes into breast milk. Therefore, where it is necessary for lactating mothers to receive Zibor, they should be advised toavoid breastfeeding.

4.7 Effects on ability to drive and use machines

Zibor has no or negligible 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 Zibor.

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:

System organ class and frequency	**Adverse reaction**
Blood and lymphatic system disorders:	
Common	Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract) which may cause haemorrhagic anaemia
Uncommon	Mild and transient thrombocytopenia (HIT type I) (see section 4.4)
	Severe thrombocytopenia (type II) (see section 4.4)
Rare	
Immune system disorders:	
Uncommon	Cutaneous allergic reactions (urticaria, pruritus)
	Anaphylactic reactions (nausea, vomiting, fever, dyspnea, bronchospasm, glottis oedema, hypotension, urticaria, pruritus)
Rare	
Metabolism and nutrition disorders:	
Not known (cannot be estimated from the available data)	Hyperkalemia (see section 4.4)

Hepatobiliary disorders: Common	Mild and transient elevations of transaminases (ASAT, ALAT) and gamma-GT levels.
Skin and subcutaneous tissue disorders: Rare	Cutaneous necrosis at the injection site (see section 4.4).
General disorders and administration site conditions: Very common Rare	 Ecchymosis at injection site. 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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

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.

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 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 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 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 determined by measuring the plasma anti-Xa activity using the amydolitic method; it is based on reference to 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 the 1st 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 2,500 IU and 3,500 IU occurs 2 to 3 hours after subcutaneous 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 5,000 IU, 7,500 IU, 10,000 IU and 12,500 IU occurs 3 to 4 hours after subcutaneous 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 7,500 IU, 10,000 IU and 12,500 IU.

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

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

Elderly: the results from a pharmacokinetic analysis of the clinical trial conducted in healthy young volunteers and elderly (> 65 years) show that there are no significant differences in the kinetic profile of bemiparin between young and elderly when 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 neither 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, Zibor should be used immediately.

6.4 Special precautions for storage

Do not store above 30º C. Do not freeze.

6.5 Nature and contents of container

0.2 ml solution in pre-filled syringe (Type I glass) with a plunger rod (polypropylene), rubber plunger stopper (chlorobutyl) and injection needle (stainless steel). Packs of 2, 6, 10, 30 and 100 syringes.

In some package sizes, the prefilled syringe may be combined to a safety device system. For syringes with safety device system the needle must be oriented away from the user and anyone else who is present. The safety system is activated by pressing firmly on the plunger rod. The protective sleeve will automatically cover the needle and will produce an audible click which confirms the activation of the device.

Immediately, the syringe must be discarded by throwing it into the nearest sharps bin (the needle in). The container lid must be closed tightly and the container placed out of the reach of children.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Single-dose 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rovi Pharma Industrial Services S.A.
Via Complutense 140
Alcala De Henares
Madrid
28805
Spain

8 MARKETING AUTHORISATION NUMBER

PA1769/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 May 2002

Date of last renewal: 09 March 2010

10 DATE OF REVISION OF THE TEXT