PROPOSED PROFESSIONAL INFORMATION - CLEAN COPY

SCHEDULING STATUS:

S4

PROPRIETARY NAME [AND DOSAGE FORM]:

Pre-filled syringes:

HIBOR 2 500 IU/0,2 ml (SOLUTION FOR INJECTION)

HIBOR 3 500 IU/0,2 ml (SOLUTION FOR INJECTION)

COMPOSITION:

HIBOR 2 500 IU/0,2 ml contains: Bemiparin sodium 2 500 IU (anti Factor Xa *) per 0,2 ml pre-filled syringe (equivalent to 12 500 IU (anti Factor Xa *) per millilitre of solution for injection).

HIBOR 3 500 IU/0,2 ml contains: Bemiparin sodium 3 500 IU (anti Factor Xa *) per 0,2 ml pre-filled syringe (equivalent to 17 500 IU (anti Factor Xa *) per millilitre of solution for injection).

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

Excipients: Water for injection

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Heparin acts as a catalyser of the ATIII enzyme, accelerating the formation of the neutralising complex with thrombin and blocking the enzyme activity of coagulation factors. ATIII inhibits both thrombin and the active form of other coagulation factors (XII, XI, IX and X), as well as plasmin. However, inhibition of thrombin and FXa is particularly significant and clinically relevant. Fractionation of the heparin molecule (4 000 – 7 000 daltons) has allowed for selecting the fractions with a lower MW (LMWHs), which retain the anti Xa activity, but have a reduced anti IIA activity.

Bemiparin sodium is a low molecular weight heparin (LMWH) obtained by depolymerisation of heparin sodium from porcine intestinal mucosa. Its mean molecular weight (MW) is approximately 3600 daltons. 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/IIA ratio is approximately 8.

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.

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

Absorption: Bemiparin sodium is 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, metabolism and excretion of bemiparin in humans.

INDICATIONS:

- Prevention of thromboembolic disease in patients undergoing general and orthopaedic surgery.
- Prevention of clotting in the extracorporeal circuit during haemodialysis.

CONTRAINDICATIONS:

Hypersensitivity to **HIBOR**, heparin or substances derived from pigs.

History of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (HIT) (see *Warnings and Special precautions).*

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

Severe impairment of liver and pancreas function

Injuries to and operations on the central nervous system, eyes and ears.

Disseminated intravascular coagulation (DIC) attributable to heparin-induced thrombocytopenia.

Acute endocarditis and endocarditis lenta.

Organic lesion with high risk of bleeding (e.g. active peptic ulcer, haemorrhagic stroke, cerebral aneurysm or cerebral neoplasms).

Safety and efficacy in children has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Do not administer by the intramuscular route.

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

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 medicines is required.

HIBOR should not be mixed with any other injections or infusions.

Caution should be exercised in patients with liver or renal 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.

HIBOR 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 taking potassium sparing medicines. The risk of hyperkalaemia appears to increase with the duration of therapy. Serum electrolytes should be measured in patients at risk before

starting **HIBOR** therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Heparin-induced thrombocytopenia:

HIBOR is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia, with or without thrombosis. The risk of heparin-induced thrombocytopenia may persist for several years. If a history of heparin-induced thrombocytopenia is suspected, the decision to use **HIBOR** in such a case must be made only in consultation with an expert in the field.

Thrombocytopenia (type I) at the beginning of therapy with **HIBOR** with platelet counts between 100,000/mm^3 and 150,000/mm^3 due to platelet activation has been observed (see *Side-effects*).

Antibody-mediated severe thrombocytopenia (type II) with platelet counts clearly below 100,000/mm^3 has been observed (see *Side-effects*). This effect usually occurs within 5 to 21 days after the beginning of treatment; in patients with a history of heparin-induced thrombocytopenia this may occur sooner.

Platelet counts are recommended before administration of **HIBOR**, on the first day of therapy and then regularly every 3 to 4 days and at the end of therapy with **HIBOR**. 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 **HIBOR**.

Cases of cutaneous necrosis, sometimes preceded by purpura or painful erythematous blotches have been reported with **HIBOR** (see *Side-effects*). In such cases, treatment should be discontinued immediately.

Spinal/Epidural anaesthesia:

In patients undergoing epidural or spinal anaesthesia or lumbar puncture, the prophylactic use of HIBOR may be associated with epidural or spinal haematomas, resulting in prolonged or permanent paralysis (see *Side effects*).

The risk is greater with higher HIBOR dosage regimens, use of post-operative indwelling catheters or by the concomitant use of medicines affecting haemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants (see *Interactions*) and by traumatic or repeated neuraxial puncture.

Placement and removal of the catheter is best performed when the anticoagulant effect of HIBOR is low. Neuraxial techniques-should be avoided in patients administered a dose of HIBOR 2 hours pre-operatively (general surgery).

When reaching a decision as to the interval between the last HIBOR 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 HIBOR.

The subsequent dose of HIBOR 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 medical practitioner 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 midline 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 medical practitioner immediately if they experience any of these symptoms. If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment including spinal decompression should be initiated.

Effects on ability to drive and operate machinery:

HIBOR has no influence on the ability to drive and use precision or dangerous machinery.

INTERACTIONS:

HIBOR interactions with other medicines have not been investigated and the information given on this section is derived from data available from other LMWH.

The concomitant administration of **HIBOR** and the following medicines is not advisable:

Vitamin K antagonists and other anticoagulants, acetyl salicylic acid and other salicylates and NSAIDs, ticlopidine, clopidogrel and other platelet inhibitors including glycoprotein IIb/IIIa antagonists; systemic glucocorticoids and dextran.

All these medicines increase the pharmacological effect of **HIBOR** 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.

Medicines that increase the serum potassium concentration should only be taken concomitantly under especially careful medical supervision.

Interaction of **HIBOR** with intravenous nitroglycerine (which can result in a decrease in efficacy) cannot be ruled out.

PREGNANCY AND LACTATION:

Safety in Pregnancy has not been established.

HIBOR is not recommended for use by women who are pregnant.

Lactation: Mothers who receive **HIBOR** should be advised to avoid breast-feeding.

DOSAGE AND DIRECTIONS FOR USE:

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.

ADULTS:

General surgery with risk of venous thromboembolism:

On the day of the surgical procedure, 2 500 IU anti Xa are to be administered by subcutaneous (sc) route, 2 hours before or 6 hours after surgery. On subsequent days, 2 500 IU anti Xa sc are to be administered every 24 hours.

Orthopaedic surgery with high risk of venous thromboembolism:

On the day of the surgical procedure, 3 500 IU anti Xa are to be administered by subcutaneous route, 2 hours before or 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 medical practitioner'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 the thromboembolic disease in non-surgical patients:

The recommended dose of **HIBOR** is 2 500 IU/day or 3 500 IU/day.

By subcutaneous route, according to whether the set of risk factors of the patients defines them as mild or high-risk thromboembolic patients.

Prophylactic treatment must be continued, according to the medical practitioner's criteria, during the risk period or until the complete mobilisation of the patient.

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.

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

Elderly: No dose adjustment required.

Renal and hepatic impairment: There is insufficient data to recommend a dose adjustment of **HIBOR** 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 **HIBOR** 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.

SIDE-EFFECTS:

The frequency of AEs reported with **HIBOR** are:

Frequently-occurring:

General disorders and administration site conditions:

- Haematoma and pain at injection site
- Ecchymosis at injection site (occurring in approximately 15% of patients receiving **HIBOR**).
- Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract)

Investigations:

- Elevations of transaminases (AST, ALT) and gamma-GT levels

Less frequently-occurring:

Skin and subcutaneous tissue disorders:

- Cutaneous allergic reactions (urticaria, pruritus)

Blood and lymphatic system disorders:

- Transient thrombocytopenia (type I) (see W*arnings and Special precautions for use*)
- Severe thrombocytopenia (type II) (see W*arnings and Special precautions for use*)

Immune system disorders:

- Anaphylactic reactions (nausea, vomiting, fever, dyspnoea, bronchospasm, glottis oedema, hypotension, urticaria, pruritus)

General disorders and administration site conditions:

- Cutaneous necrosis at the injection site (see W*arnings and Special precautions for use*)

Nervous system disorders:

- Epidural and spinal haematoma following epidural or spinal anaesthesia and lumbar puncture. These haematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see W*arnings and Special precautions for use*).

Musculoskeletal and connective tissue disorders:

- Osteoporosis (associated with long-term heparin treatment)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Bleeding is the main symptom of overdose. **HIBOR** should be discontinued. In case of major haemorrhages, administration of protamine sulphate may be needed. 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.

IDENTIFICATION:

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

PRESENTATION:

0,2 ml of solution in a 0,5 ml pre-filled syringe (transparent, Type I borosilicated glass) with a yellow

(2 500 IU/0,2 ml) or red (3 500 IU/0,2 ml), rubber plunger rod (non-siliconised polypropylene), black, rubber plunger-stopper (Type I chloro butyl rubber) and injection needle (class AISI 304 passivated stainless steel), with a natural rubber tip cap. Packs of 2, 10, 30 and 100 syringes.

INSTRUCTIONS FOR USE/HANDLING:

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 product and injection needles should be disposed of in accordance with local requirements.

STORAGE INSTRUCTIONS:

Store at or below 25°C. Do not freeze. After first opening, **HIBOR** should be used immediately.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

Pre-filled syringes:

HIBOR 2 500 IU/0,2 ml: A40/8.2/0234

HIBOR 3 500 IU/0,2 ml: A40/8.2/0235

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zimbili Pharma CC

24 Parrot Avenue,

Extension 1,

Lenasia 1827,

South Africa

DATE OF REGISTRATION:

11 June 2018

DATE OF PUBLICATION OF THE PACKAGE INSERT:

31 October 2017.

PROPOSED PROFESSIONAL INFORMATION - CLEAN COPY

SCHEDULING STATUS:

S4

PROPRIETARY NAME [and dosage form]:

Pre-filled syringes:

HIBOR 5 000 IU/0,2 ml (solution for injection)

HIBOR 7 500 IU/0,3 ml (solution for injection)

HIBOR 10 000 IU/0,4 ml (solution for injection)

COMPOSITION:

HIBOR 5 000 IU/0,2 ml contains: Bemiparin Sodium 5 000 IU (anti Factor Xa *) per 0,2 ml pre-filled syringe [equivalent to 25 000 IU (anti Factor Xa *) per millilitre of solution for injection.]

HIBOR 7 500 IU/0,3 ml contains: Bemiparin Sodium 7 500 IU (anti Factor Xa *) per 0,3 ml pre-filled syringe [equivalent to 25 000 IU (anti Factor Xa *) per millilitre of solution for injection.]

HIBOR 10 000 IU/0,4 ml contains: Bemiparin Sodium 10 000 IU (anti Factor Xa *) per 0,4 ml pre-filled syringe [equivalent to 25 000 IU (anti Factor Xa *) per millilitre of solution for injection.]

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

Excipients: Water for Injection.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Heparin acts as a catalyser of the ATIII enzyme, accelerating the formation of the neutralising complex with thrombin and blocking the enzyme activity of coagulation factors. ATIII inhibits both thrombin and the active form of other coagulation factors (XII, XI, IX and X), as well as plasmin. However, inhibition of thrombin and FXa is particularly significant and clinically relevant. Fractionation of the heparin molecule (4 000–7 000 daltons) has allowed for selecting the fractions with a lower MW (LMWHs), which retain the anti Xa activity, but have a reduced anti IIA activity.

Bemiparin sodium is a low molecular weight heparin (LMWH) obtained by depolymerisation of heparin sodium from porcine intestinal mucosa. Its mean molecular weight (MW) is approximately 3 600 daltons. 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/IIA ratio is approximately 8.

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.

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

Absorption:

Bemiparin sodium is 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, metabolism and excretion of bemiparin in humans.

INDICATIONS:

The treatment of established deep vein thrombosis, with or without pulmonary embolism.

CONTRAINDICATIONS:

Hypersensitivity to **HIBOR**, heparin or substances derived from pigs.

History of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (HIT) (see WARNINGS AND SPECIAL PRECAUTIONS).

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

Severe impairment of liver and pancreas function

Injuries to and operations on the central nervous system, eyes and ears.

Disseminated intravascular coagulation attributable to heparin-induced thrombocytopenia.

Acute endocarditis and endocarditis lenta

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 contra-indicated.

Safety and efficacy in children has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Do not administer by the intramuscular route.

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

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 medicines is required.

HIBOR should not be mixed with any other injections or infusions.

Caution should be exercised in patients with liver or renal 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.

HIBOR 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 taking potassium sparing medicines. The risk of hyperkalaemia appears to increase with the duration of therapy. Serum electrolytes should be measured in patients at risk before starting **HIBOR** therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days.

Heparin-induced thrombocytopenia:

HIBOR is to be used with extreme caution in patients with a history of heparin-induced thrombocytopenia, with or without thrombosis. The risk of heparin-induced thrombocytopenia may persist for several years. If a history of heparin-induced thrombocytopenia is suspected, the decision to use **HIBOR** in such a case must be made only in consultation with an expert in the field.

Thrombocytopenia (type I) at the beginning of therapy with heparin with platelet counts between 100,000/mm^3 and 150,000/mm_3 due to platelet activation has been observed (see SIDE-EFFECTS). Antibody-mediated severe thrombocytopenia (type II) with platelet counts clearly below 100,000/mm^3 has been observed (see SIDE-EFFECTS). This effect usually occurs within 5 to 21 days after the beginning of treatment; in patients with a history of heparin-induced thrombocytopenia this may occur sooner.

Platelet counts are recommended before administration of **HIBOR**, on the first day of therapy and then regularly every 3 to 4 days and at the end of therapy with **HIBOR**. 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 **HIBOR**.

Cases of cutaneous necrosis, sometimes preceded by purpura or painful erythematous blotches have been reported with **HIBOR** (see SIDE-EFFECTS). In such cases, treatment should be discontinued immediately.

Spinal/Epidural anaesthesia:
In patients undergoing epidural or spinal anaesthesia or lumbar puncture, the prophylactic use of HIBOR may be associated with epidural or spinal haematoma, resulting in prolonged or permanent paralysis (see *Side effects*). **The risk is greater with higher HIBOR dosage regimens, use of post-operative indwelling catheters or by the concomitant use of medicines affecting haemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants (see INTERACTIONS) and by traumatic or repeated neuraxial puncture.**
Placement and removal of the catheter is best performed when the anticoagulant effect of HIBOR is low. Neuraxial techniques-should be avoided in patients administered a dose of HIBOR 2 hours pre-operatively (general surgery).
When reaching a decision as to the interval between the last HIBOR 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 HIBOR. The subsequent dose of HIBOR 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 medical practitioner 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 midline 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 medical practitioner immediately if they experience any of these symptoms. If signs or symptoms of epidural or spinal haematoma are suspected, urgent diagnosis and treatment including spinal decompression should be initiated.

Effects on ability to drive and operate machinery:

HIBOR has no influence on the ability to drive and use precision or dangerous machinery.

INTERACTIONS:

HIBOR interactions with other medicines have not been investigated and the information given on this section is derived from data available from other LMWH.

The concomitant administration of **HIBOR** and the following medicines is not advisable:

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

All these medicines increase the pharmacological effect of **HIBOR** 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.

Medicines that increase the serum potassium concentration should only be taken concomitantly under especially careful medical supervision.

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

PREGNANCY AND LACTATION:

Safety in Pregnancy has not been established.

HIBOR is not recommended for use by women who are pregnant.

Lactation: Mothers who receive **HIBOR** should be advised to avoid breast-feeding.

DOSAGE AND DIRECTIONS FOR USE:

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.

ADULTS:

Treatment of deep vein thrombosis:

HIBOR 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 pre-filled 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 contra-indication, oral anticoagulation should be commenced 3-5 days after beginning **HIBOR** first administration, and the dose adjusted so as to keep the International Normalised Ratio (INR) value between 2-3 times the control value. **HIBOR** 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 **HIBOR** 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 **HIBOR** 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 **HIBOR** 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.

SIDE-EFFECTS:

The frequency of AEs reported with **HIBOR** are:

Frequently-occurring:

General disorders and administration site conditions:

- Haematoma and pain at injection site

- Ecchymosis at injection site (occurring in approximately 15 % of patients receiving **HIBOR**)
- Bleeding complications (skin, mucous membranes, wounds, gastro-intestinal tract, urogenital tract)

Investigations:

- Elevations of transaminases (AST, ALT) and gamma-GT levels

Less frequently-occurring:

Skin and subcutaneous tissue disorders:

- Cutaneous allergic reactions (urticaria, pruritus)

Blood and lymphatic system disorders:

- Transient thrombocytopenia (type I) (see W*arnings and Special precautions for use*)
- Severe thrombocytopenia (type II) (see W*arnings and Special precautions for use*)

Immune system disorders:

- Anaphylactic reactions (nausea, vomiting, fever, dyspnoea, bronchospasm, glottis oedema, hypotension, urticaria, pruritus)

General disorders and administration site conditions:

- Cutaneous necrosis at the injection site (see WARNINGS and SPECIAL PRECAUTIONS FOR USE)

Nervous system disorders:

- Epidural and spinal haematoma following epidural or spinal anaesthesia and lumbar puncture. These haematomas have caused various degrees of neurological impairment, including prolonged or permanent paralysis (see WARNINGS and SPECIAL PRECAUTIONS FOR USE)

Musculoskeletal and connective tissue disorders:

- Osteoporosis (associated with long-term heparin treatment)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Bleeding is the main symptom of overdose. **HIBOR** should be discontinued. In case of major haemorrhages, administration of protamine sulphate may be needed. 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.

IDENTIFICATION:

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

PRESENTATION:

0,2 ml, 0,3 ml and 0,4 ml of solution in a 0,5 ml pre-filled syringe (transparent, Type I borosilicated glass) with a natural, rubber plunger rod (non-siliconised polypropylene), black, rubber plunger-stopper (Type I chloro butyl rubber) and injection needle (class AISI 304 passivated stainless steel), with a natural rubber tip cap. Packs of 2, 10, 30 and 100 syringes.

INSTRUCTIONS FOR USE/HANDLING:

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 product and injection needles should be disposed of in accordance with local requirements.

STORAGE INSTRUCTIONS:

Store at or below 25°C. Do not freeze. After first opening, **HIBOR** should be used immediately.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

Pre-filled syringes:

HIBOR 5 000 IU/0,2 ml: A40/8.2/0236

HIBOR 7 500 IU/0,3 ml: A40/8.2/0237

HIBOR 10 000 IU/0,4 ml: A40/8.2/0238

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zimbili Pharma CC

24 Parrot Avenue,

Extension 1,

Lenasia 1827,

South Africa

DATE OF REGISTRATION:

11 June 2018

DATE OF PUBLICATION OF THE PACKAGE INSERT:

31 October 2017