HIBOR®
Bemiparin, INN
Second Generation
Low Molecular Weight Heparin
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1. Obtention and chemical structure

HIBOR® (Bemiparin) is a low molecular weight heparin (LMWH) originating from unfractionated heparin (UFH) from porcine intestinal mucosa\textsuperscript{1,2}. It is obtained as a sodium salt from the fractioning of UH using a patented depolymerization method through beta-elimination in a non-aqueous medium, unlike other forms of beta-elimination\textsuperscript{1-3}.

The chemical structure of HIBOR® (Bemiparin) gives it certain qualities and characteristics that make it distinctive from other LMWHs\textsuperscript{2,3} and it is the basis for it to be considered as the first representative of the second generation of LMWHs\textsuperscript{2,3}. It is characterized by presenting a group 4-enolpyranosyl uronate on its non-reducing end (Figure 1)\textsuperscript{1}.

Figure 1. Chemical structure of HIBOR® (Bemiparin)\textsuperscript{1}

HIBOR® (Bemiparin) has a mean molecular weight (MW) of 3,600 Daltons (D), the lowest of the low molecular weight heparins currently on the market\textsuperscript{2,4}. The exclusive and innovative method for obtaining it allows an optimal distribution of the fragments: 74.6% has a MW of between 2,000 and 6,000 D; the percentage of fragments with a MW greater than 6,000 D is much lower than with the other LMWHs and most of the fragments are shorter than the critical length (Figure 2)\textsuperscript{5}.

Figure 2. Mean MW and percentage distribution of the LWMHs\textsuperscript{2,4,5}

<table>
<thead>
<tr>
<th>Mean MW (D)</th>
<th>HIBOR (Bemiparin)</th>
<th>Enoxaparin</th>
<th>Nadroparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chemical structure of HIBOR® provides it certain qualities and characteristics that make it distinctive from other LMWHs and it is the basis for it to be considered as the first representative of the second generation of LMWHs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The comparison between the chromatographs of HIBOR® (Bemiparin) and other LMWHs highlights the differences in the distribution of the MW of the fragments. As can be seen in Figure 3, the chromatograph of HIBOR® (Bemiparin) appears biased towards the lower MW and its greater height corresponds to the MW fragments included between 2,000 and 6,000 D, the most abundant\textsuperscript{3}.

Figure 3. Chromatograph of HIBOR® (Bemiparin) and other LMWHs\textsuperscript{3}

HIBOR® (Bemiparin)
Nadroparin
Dalteparin
Enoxaparin

Molecular weight (K.D.)
2. Mechanism of action

2.1 ANTI-THROMBOTIC ACTIVITY

HIBOR® (Bemiparin) has an anti-coagulant mechanism of action similar to that of other LMWHs but it presents unique features. The distribution of the LMWHs fragments has been investigated in vitro. It has a direct influence on the ratio of their anti-FXa/anti-FIIa activity, which indicates the ratio between the anti-thrombotic benefit and the risk of haemorrhage.

HIBOR® (Bemiparin) has an anti-FXa activity of between 80 and 110 IU/mg and its anti-FIIa activity is from 5-10 IU/mg; therefore, its inhibitory effect on Factor Xa is at least eight times greater than on Factor IIa. As a result, the anti-FXa/anti-FIIa activity ratio is 8:1, the best in comparison with the first generation LMWHs and in comparison with UFH (Table 1).

Table 1. Ratio of the anti-FXa/anti-FIIa activity of the LMWHs currently marketed in Spain

<table>
<thead>
<tr>
<th>First generation LMWHs</th>
<th>HIBOR® (Bemiparin)</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Enoxaparin</th>
<th>Nadroparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-FXa/ Anti-FII ratio</td>
<td>8:1</td>
<td>2.5:1</td>
<td>2:1</td>
<td>2.7:1</td>
<td>3.2:1</td>
</tr>
</tbody>
</table>

2.2 RELEASE OF TFPI

Factor Xa may also be inhibited by the tissue factor pathway inhibitor (TFPI). The role played by the Tissue Factor (TF) as the most important factor in the onset of plasma coagulation has been known for many years, but it has been over the last 20 years that scientists have come to understand in greater detail its complexity and cell biology.

HIBOR® shows an anti-FXa/anti-FIIa activity ratio of 8:1, the best in comparison with the first generation LMWHs and in comparison with UFH.

TFPI is a natural coagulation inhibitor synthesized by endothelium and monocytes and has been shown to be a good marker of endothelial lesion. It is released from these cells after exposure to heparin.
Various studies have shown the increase of TFPI levels produced by the administration of heparin5-14. Heparin induces the release of TFPI from the endogenous deposits in the vessel wall, probably through the anionic charge of its molecule. It is of interest to note the greater efficacy of the LMWHs over UH due to the different effect on TFPI, as it produces a more noticeable increase12,13.

HIBOR® (Bemiparin) has shown its action through the TFPI pathway15-17 where it produces a considerable increase in release, thus contributing to its anti-thrombotic effect15-17.

In a recent study17 HIBOR® (Bemiparin) was shown to regulate the expression, release and activity of TFPI in endothelial cells with greater efficacy than UFH or Dalteparin. For this reason, HIBOR® (Bemiparin) might be superior to other conventional heparins for maintaining the anticoagulant properties of the endothelium (Figure 4).

![Figure 4](image)

**Figure 4**

Release of TFPI in the medium (ng/10^6 cells)
TFPI in lysed cells (ng/10^6 cells)
Activity of TFPI on the surface (ng/10^6 cells)

C=Control Cells  B=Bemiparin  D=Dalteparin  H=UFH

**2.3 ANTI-COAGULANT ACTIVITY**

The ability to produce an effective anti-thrombotic effect with a lower risk of haemorrhagic complications is a potential advantage of the LMWHs over UFH. Because of the unique molecular structure which gives HIBOR® (Bemiparin) a better anti-FXa/anti-FIIa activity ratio (please see Table 1), it may improve this advantage over other LMWHs3.

The haemorrhagic effect of HIBOR® (Bemiparin) was compared with that of two LMWHs, Enoxaparin and Dalteparin. The products were administered to rats endovenously at doses of 2, 4 and 8 mg/kg and the volume extravasated through gastric mucosa over the 20 minutes of the trial was determined1. In intravenous administration, all three drugs turned out to have a dose-dependent anti-coagulant effect; the haemorrhagic effect of HIBOR® (Bemiparin) was, however, significantly lower1.
3. Pharmacokinetics

3.1 BIOAVAILABILITY

HIBOR® (Bemiparin) is absorbed into the subcutaneous deposit and quickly reaches the bloodstream\textsuperscript{18}. Its bioavailability is practically total (96%), allowing a single daily dose for prophylaxis of peri-operative venous thromboembolism\textsuperscript{18}.

3.2 PHARMACOKINETIC PROFILE OF HIBOR® (BEMIPARIN)

The pharmacokinetic profile of the different doses of HIBOR® (Bemiparin) was determined in various studies using healthy volunteers; two with an open-label, three-arm, cross-over design and one with a randomized, open-label, comparative with Enoxaparin, with a wash-out period of one week between each treatment (Table II)\textsuperscript{16,18-20}.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Dose of HIBOR® (Bemiparin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falkon L, et al.\textsuperscript{18}</td>
<td>2,500 IU (sc) 5,000 IU (sc) 5,000 IU (iv)</td>
</tr>
<tr>
<td>Fontcuberta J, et al.\textsuperscript{19}</td>
<td>3,500 IU (sc)</td>
</tr>
<tr>
<td>Falkon L, et al.\textsuperscript{20}</td>
<td>7,500 IU (sc) 10,000 IU (sc) 12,500 IU (sc)</td>
</tr>
</tbody>
</table>
3.2.1 Pharmacokinetic profile of anti-FXa activity

There is currently no adequate method available to determine plasma concentration of heparins; for this reason, the pharmacokinetic parameters of HIBOR® (Bemiparin) were calculated using the determination of the anti-FXa activity in a series of blood samples obtained over the 24 hours following administration of the dose (Table III)\(^{16,18-20}\).

In the first trial\(^{16,18}\), in 12 healthy volunteers, each subject received HIBOR® (Bemiparin) at doses of 2,500 IU subcutaneously, 5,000 IU subcutaneously and 5,000 IU intravenously. In the intravenous route of administration, 5,000 IU of HIBOR® (Bemiparin) produces a peak of anti-FXa activity (\(E_{\text{max}} = 1.30 \pm 0.18\) IU/ml) within the 3 minutes following administration.

The bioavailability of HIBOR® (Bemiparin) is practically total, allowing a single dose for prophylaxis and treatment of VTED

<table>
<thead>
<tr>
<th>Dose (sc)</th>
<th>AUC (IU/ml h-1)</th>
<th>(E_{\text{max}}) (IU/ml)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(T_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,500 IU</td>
<td>2.02 ± 0.53</td>
<td>0.34 ± 0.08</td>
<td>2-3</td>
<td>5.31 ± 1.59</td>
</tr>
<tr>
<td>3,500 IU</td>
<td>3.78 ± 0.87</td>
<td>0.45 ± 0.07</td>
<td>2-4</td>
<td>5.44 ± 1.60</td>
</tr>
<tr>
<td>5,000 IU</td>
<td>4.70 ± 0.58</td>
<td>0.54 ± 0.06</td>
<td>3-4</td>
<td>5.29 ± 1.12</td>
</tr>
<tr>
<td>7,500 IU</td>
<td>12.82 ± 2.27</td>
<td>1.22 ± 2.27</td>
<td>3-6</td>
<td>5.19 ± 1.32</td>
</tr>
<tr>
<td>10,000 IU</td>
<td>16.55 ± 2.18</td>
<td>1.42 ± 0.19</td>
<td>3-6</td>
<td>5.44 ± 0.49</td>
</tr>
</tbody>
</table>

With subcutaneous administration, the \(E_{\text{max}}\) values were lower with both the 2,500 IU dose (\(E_{\text{max}} = 0.34 \pm 0.08\) IU/ml) and also the 5,000 IU dose (\(E_{\text{max}} = 0.54 \pm 0.06\) IU/ml), with these levels being achieved between 2 and 4 hours after administration. The anti-FXa activity was detected in a period of 12 to 18 hours after subcutaneous administration of HIBOR® (Bemiparin) (Figure 5)\(^{16,18}\).
In another complementary study\textsuperscript{19}, 12 healthy volunteers were analyzed for the pharmacokinetics parameters of HIBOR\textsuperscript{®} (Bemiparin) administered at a subcutaneous dose of 3,500 IU (Figure 6). An $E_{\text{max}}$ value of 0.45 ± 0.07 IU/ml was obtained, appropriate for thromboembolic prophylaxis in high-risk patients (please see Table III).

The anti-FXa activity figures for HIBOR\textsuperscript{®} (Bemiparin) at doses of 2,500, 3,500 and 5,000 IU subcutaneously demonstrate the product's linear pharmacokinetic profile and, therefore, the correspondence between the dose administered and the anti-thrombotic activity (please see Figures 5 and 6)\textsuperscript{16,18,19}.

In a later study\textsuperscript{20} high doses (7,500 IU, 10,000 IU and 12,500 IU) of HIBOR\textsuperscript{®} (Bemiparin) were administered subcutaneously to 12 healthy volunteers. The values of the pharmacokinetic parameters of HIBOR\textsuperscript{®} (Bemiparin) in terms of its anti-FXa activity are given in Table III.

The anti-FXa activity follows the same pattern as in previous trials, it is dose-dependent with a first-order kinetics. This anti-FXa activity appears at an early
stage in the first 30 minutes and peaks between 3 and 4 hours after administration of the dose (Figure 7).

3.2.2 Pharmacokinetic profile of the activity on TFPI

The effect of HIBOR® (Bemiparin) on TFPI was also determined in these trials. Unlike the anti-FXa activity, which is dose-dependent, the effect on TFPI was similar for the different doses and routes of administration. This may be due to the fact that the lowest dose of HIBOR® (Bemiparin) is capable of releasing the entire pool of TFPI that the heparins can release. Although the anti-FXa activity lasts for up to 18 hours, the effect on TFPI appears sooner, but lasts for only from 6 to 8 hours. The anti-thrombotic anti-FXa activity is anticipated and enhanced by the TFPI effect.

The effect of high doses of HIBOR® (Bemiparin) administered subcutaneously on the release of TFPI was similar to that obtained with lower doses, confirming that the response is independent of the amount of drug present in the bloodstream.

In summary, HIBOR® (Bemiparin) exerts its anti-FXa activity through the action of the TFPI during the first two hours after administration, through its actions on antithrombin III and TFPI simultaneously for the next eight hours (range 2-10 hours) and through antithrombin III for the last eight hours (range 10-18 hours).

3.2.3 Pharmacokinetic profile of the anti-FIIa activity

The anti-FIIa activity was minimal (0.013 IU/ml) 10 minutes after intravenous administration of HIBOR® (Bemiparin) and was not detectable after subcutaneous administration. Although the anti-FIIa activity was significantly greater with the highest doses of HIBOR® (Bemiparin) (10,000 and 12,500 IU) the difference was marginal. The mean anti-FXa activity was approximately 100 times greater than the anti-FIIa activity. These results clearly show that HIBOR® (Bemiparin) has differing effects as an anti-FXa and as anti-FIIa agent.
3.2.4 Modification of the activated partial thromboplastin time (aPTT)

The ratio of aPTT reached a peak of $1.61 \pm 0.24$ five minutes after intravenous administration of 5,000 IU, returning to basal values in 12 hours. Similarly, the subcutaneous administration of 2,500 IU and 5,000 IU of HIBOR® (Bemiparin) produced a slight but significant increase in the aPTT ratio of $1.24 \pm 0.13$ and $1.26 \pm 0.18$ minutes respectively\(^{18}\). Through this route, the aPTT ratio peaked two hours after administration but recovered baseline values within the next 12 hours\(^{18}\).

**HIBOR® has a selective anti-FXa activity with respect to the anti-FIIa activity**

3.3 PLASMA HALF-LIFE

In these trials\(^{18-20}\), the pharmacokinetic profile of HIBOR® (Bemiparin) suggests that an adequate anti-coagulant effect can be achieved over 18 hours after subcutaneous administration. Its elimination half-life (5.3 hours) is the longest of all of the LMWHs marketed in Spain (Table IV)\(^{3,4}\).

*Table IV. Plasma half-lives of the LMWHs marketed in Spain*\(^ {3,4}\)

<table>
<thead>
<tr>
<th>First generation LMWHs</th>
<th>HIBOR® (Bemiparin)</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
<th>Enoxaparin</th>
<th>Nadroparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (h)</td>
<td>5.3</td>
<td>2.2</td>
<td>1.5</td>
<td>2.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>
4. Clinical experience with HIBOR® (Bemiparin)

HIBOR® (Bemiparin) has been investigated in four large clinical trials, as well as in various pharmacoepidemiological studies (Table V). These clinical trials have allowed HIBOR® (Bemiparin) to obtain various innovative indications and recognition in Europe.

The clinical experience with HIBOR® (Bemiparin) is described below for each indication together with the investigation lines in progress.

Table V. Major clinical trials of HIBOR® (Bemiparin) in thromboembolic disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Design</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro Quilis A et al. 21,22</td>
<td>Thromboembolic prophylaxis in total knee arthroplasty</td>
<td>MC, R, DB, sequential</td>
<td>381</td>
</tr>
<tr>
<td>Kakkar VV et al. 23</td>
<td>Thromboembolic prophylaxis in total hip arthroplasty</td>
<td>MC, R, DB</td>
<td>298</td>
</tr>
<tr>
<td>Kakkar VV et al. 24-26</td>
<td>Treatment of established deep vein thrombosis and secondary prevention of recurrences</td>
<td>MC, R, DB, with masking of end point assessment</td>
<td>378</td>
</tr>
<tr>
<td>Planès et al. 27</td>
<td>Thromboembolic prophylaxis in total hip arthroplasty</td>
<td>MC</td>
<td>64</td>
</tr>
<tr>
<td>Moreno et al. 28</td>
<td>Thromboembolic prophylaxis in abdominal surgery</td>
<td>MC, R, DB</td>
<td>184</td>
</tr>
<tr>
<td>Hidalgo M et al. 29</td>
<td>Thromboembolic prophylaxis in abdominal surgery</td>
<td>MC, PHE</td>
<td>203</td>
</tr>
<tr>
<td>Fenollosa J et al. 30</td>
<td>Thromboembolic prophylaxis in orthopaedic surgery</td>
<td>MC, PhE</td>
<td>347</td>
</tr>
<tr>
<td>Bonal J et al. 31</td>
<td>Thromboembolic prophylaxis in total hip arthroplasty</td>
<td>MC, PhE, comparative</td>
<td>123</td>
</tr>
</tbody>
</table>

R: randomized; DB: Double blind; PhE: Pharmacoepidemiological; MC: Multi-centric
For surgical patients, levels of risk of thromboembolic disease have been established according to the presence of clinical risk factors (for example, prolonged immobilization, cancer, obesity) and associated with the intervention (Table VI)\textsuperscript{32}.

**Table VI. Levels of risk of thromboembolic disease\textsuperscript{32}**

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Minor surgery, major surgery in patients &lt; 40 years of age without additional risk factors</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Minor surgery in patients &gt; 40 years of age with additional risk factors</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients &lt; 40 years of age without additional risk factors</td>
</tr>
<tr>
<td></td>
<td>Non-major surgery in patients between 40 and 60 years of age without additional risk factors</td>
</tr>
<tr>
<td>High risk</td>
<td>Non-major surgery in patients &gt; 60 years of age or with additional risk factors</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients &gt; 40 years of age or with additional risk factors</td>
</tr>
<tr>
<td>Very high risk</td>
<td>Major surgery in patients &gt; 40 years of age with a history of venous thromboembolic disease, cancer or hypercoagulability</td>
</tr>
<tr>
<td></td>
<td>Knee or hip arthroplasty</td>
</tr>
<tr>
<td></td>
<td>Hip fracture surgery</td>
</tr>
<tr>
<td></td>
<td>Major trauma</td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury</td>
</tr>
</tbody>
</table>

The incidence of thromboembolic disease (VTED) in orthopaedic surgery is high in general terms. In hip replacement surgery without prophylaxis, the mean incidence of deep vein thrombosis (DVT) is 51% and that of pulmonary embolism (PE) varies between 0.7% and 30%\textsuperscript{33}. In knee replacement surgery, the incidence of DVT after arthroplasty varies between 40% and 84% and the episodes of PE from 1.8% and 7%\textsuperscript{33}. In the view of these data and of exhaustive reviews, the consensus conferences recommend prophylaxis for VTED in orthopaedic surgery of the lower limbs\textsuperscript{33}.

**HIBOR\textsuperscript{®} (Bemiparin)** has been shown to be effective as prophylaxis for VTED in both hip and knee arthroplasty, including the novelty of a new post-operative protocol\textsuperscript{21-23,27,30,31}. 


5.1 POST-OPERATIVE THROMBOEMBOLIC PROPHYLAXIS WITH HIBOR® (BEMIPARIN)

5.1.1 Reasons for a new post-operative dosage protocol

At the present time, more than 50% of the orthopaedic surgery interventions in the lower limbs are carried out with local and regional anaesthesia. Over the last few years, publications have highlighted the risk of haemorrhagic complications of the intradural or epidural punctures in patients who have been given LMWHs. This complication is rare, Tryba et al estimated its incidence at 1:150,000 with epidural anaesthesia and 1:200,000 with intradural anaesthesia. But the consequences and sequelae it produces are very severe, requiring strict neurological monitoring and, in most cases, urgent intervention in order to remove the haematoma. Each epidural haematoma is a tragedy for both the patient and the anaesthesiologist. For this reason there is controversy over the suitability of initiating anti-thrombotic prophylaxis with LMWHs in the pre- or post-operative phase with this type of anaesthesia.

In this sense, both medical societies and consensus discussion groups as well as the health-care authorities of various countries (FDA, European Medicines Agency) have given recommendations on the prophylaxis of thromboembolic disease in patients under epidural/spinal anaesthesia. In Spain the Spanish Medicines Agency (AEM in its Spanish acronym) has determined the inclusion of a new section on warnings and special usage precautions in the Data Sheets of all UFH and LMWHs. This text indicates that at least 12 hours (in the case of LMWHs) or 4 hours (in the case of UFH) must pass between the administration of the prophylactic dose and the insertion or withdrawal of the anaesthesia catheter. Once the catheter has been inserted or withdrawn, at least another four hours must pass before the administration of a further dose of heparin. The next dose will be delayed until the surgical intervention has been completed.

Where it is necessary to administer anti-coagulant therapy during a spinal/epidural anaesthetic procedure, the doctor and other members of the medical team must monitor the situation with the maximum attention to be able to detect any symptom of neurological deficit.

On this basis, an LMWH with a good efficacy and safety profile and the possibility of initiating prophylaxis in the post-operative stage might represent a great advantage in clinical practice.
5.1.2 Thromboembolic prophylaxis beginning post-operatively in total arthroplasty of the hip

In order to be able to assess the efficacy and safety profile of 3,500 IU of HIBOR® (Bemiparin) administered as a single daily dose, beginning prophylaxis 6 hours after the end of the intervention, a trial was designed in patients subjected to total hip arthroplasty. A total of 65 patients of both sexes were recruited, all over the age of 45 years and scheduled for primary total hip replacement surgery in two hospital centres. The assessment of efficacy was made using bilateral phlebography of the lower limbs performed on the 10th day after the operation.

Figure 8. Incidence of thromboembolic events with the two treatment protocols

Incidence of thromboembolic events (%)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>HIBOR® 3,500 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASSICAL</td>
<td>2 hours before the intervention Kakkar VV et al 2000&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>NEW</td>
<td>6 hours after the intervention Planès et al 2001&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Seven of the initial patients were excluded due to the impossibility of performing the phlebography correctly, so the population which could be assessed was 57 subjects. Four cases of DVT were detected (4/57; 7.02%; CI 95%: 0.4-13.7), of which 3/57 cases were proximal DVT (5.26%; CI 95%: 0-11.1). These results were similar to those found in the study by Kakkar et al<sup>23</sup> with HIBOR® (Bemiparin) at the same dose with administration being started 2 hours prior to the intervention (Figure 8). With this post-operative dosage regimen, no major haemorrhages were observed and the incidence of haematoma at the injury site was low.

In conclusion, this study showed that 3,500 IU of HIBOR® (Bemiparin) can be administered 6 hours after surgery, showing a favourable ratio of efficacy and security. Nonetheless, in order to confirm these results, another similar study was carried out in a larger number of patients, as described below.

5.1.3 Thromboembolic prophylaxis starting post-operatively in total knee replacement (Comparative study of HIBOR® (Bemiparin) 3,500 IU post-operatively and Enoxaparin 40 mg pre-operatively)

In this randomized, multi-centric, sequential, double-blind trial in parallel groups, 381 consecutive patients over 18 years of age and scheduled for total knee arthroplasty were recruited.

The main goal was to compare the anti-thrombotic efficacy of 3,500 IU of HIBOR® (Bemiparin) administered subcutaneously once a day with prophylaxis starting 6 hours post-operatively in comparison with 40 mg of Enoxaparin subcutaneously...
once a day with prophylaxis starting 12 hours prior to surgery. As a secondary goal, the safety parameters associated with haemorrhagic events were compared.

- **Analysis of the efficacy parameters**

In the efficacy analysis, the “intention to treat” (ITT) population was 333 patients, those with at least one dose of study medication who had had a measurable phlebogram and pulmonary angiography, with symptoms of DVT and a measurable Doppler ultrasound test performed. The “per protocol” population (PP) was 324 patients, after exclusion of those who did not meet any of the criteria indicated above. The number of patients in whom the safety criteria were assessed (they had received at least one dose of study medication) was 380.

**HIBOR® 3,500 IU can be administered 6 hours after surgery showing a favourable ratio of efficacy and safety**

The combined incidence of thromboembolic disease† in the ITT population (n = 333) was 32.1% (53/165) in the HIBOR® (Bemiparin) group in comparison with 36.9% (62/168) in the Enoxaparin group (CI 95.3% = -15.1 to 5.6%; non-inferiority p = 0.02; superiority p = 0.36; Figure 9). In the PP population (n = 324), the respective data were 32.5% (52/160) in the HIBOR® (Bemiparin) group and 36.6% (60/164) in the Enoxaparin group (CI 95.3%: -14.6 to 6.4%; non-inferiority p = 0.03; superiority p = 0.44). These data show the non-inferiority of HIBOR® (Bemiparin) versus Enoxaparin.

The combined incidence of proximal DVT, non-fatal PE and/or VTED-related death in the PP population (n = 324), defined as an additional efficacy variable, was 1.9% in the HIBOR® (Bemiparin) group and 5.5% in the Enoxaparin group (non-inferiority p = 0.02).

Furthermore, the isolated incidence of proximal DVT was lower in the patients treated with HIBOR® (Bemiparin) than in those who received Enoxaparin (1.8% versus 4.2% respectively) (Figure 9).

**Figure 9. Combined incidence of venous thromboembolic disease (VTED) and proximal deep vein thrombosis (DVT) in total knee arthroplasty**

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Enoxaparin, 40 mg (n = 168)</th>
<th>12 hours prior to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIBOR® 3,500 IU (n = 165)</td>
<td>6 hours after surgery</td>
</tr>
</tbody>
</table>

† Combined incidence of VTED = total DVT and/or non-fatal PE and/or death by any cause.
• Analysis of the safety parameters

The incidence of haemorrhagic events in both groups (3.7%) did not show any significant differences in the events considered major nor in the minor ones. Nor were there any significant differences in the blood losses during the operation (volume of blood transfused plus uncompensated losses).

Nonetheless, a significant difference was observed in the incidence of haematomas at the injection site, 32.5% in the case of Enoxaparin in comparison with 22.7% in the HIBOR® (Bemiparin) group (p = 0.03; Figure 10).

The results of the analytical parameters did not show significant differences between the two groups.

• Conclusions

A set dose of 3,500 IU of HIBOR® (Bemiparin) administered every 24 hours, with prophylaxis starting 6 hours after surgery, is as effective and safe as 40 mg of Enoxaparin administered every 24 hours, with prophylaxis starting 12 hours before surgery, for the prevention of the combined incidence of VTED in patients subjected to total arthroplasty of the knee.

Figure 10. Incidence of haematomas at the injection site

Incidence (%)

40 mg of Enoxaparin 12 hours before surgery

3,500 IU of HIBOR® (Bemiparin) 6 hours after surgery

*p=0.03 3,500 IU of HIBOR® (Bemiparin) versus 40 mg of Enoxaparin

This new post-operative protocol for the prophylaxis of VTED make it easier to perform techniques with local and regional anaesthesia, minimizing the risk of spinal haemorrhagic complications.
5.2 PRE-OPERATIVE THROMBOEMBOLIC PROPHYLAXIS WITH HIBOR® (BEMIPARIN)

5.2.1 Thromboembolic prophylaxis starting pre-operatively in total arthroplasty of the hip\textsuperscript{23} (Comparative study between 3,500 IU of HIBOR® (Bemiparin) and UFH).

In a randomized double-blind trial, 298 patients at high risk of thromboembolism and subjected to total hip replacement were included. They were treated with 3,500 IU of HIBOR® (Bemiparin) administered subcutaneously once a day starting 2 hours pre-operatively or with 5,000 IU of unfractionated heparin subcutaneously twice a day and continuing for an average of 12 days during the post-operative period. Most of the patients received general anaesthesia during the intervention.

- Analysis of the efficacy parameters

The incidence of thromboembolic events, confirmed by venography, was significantly lower in the group treated with 3,500 IU of HIBOR® (Bemiparin) than in the group treated with UFH (7.2% versus 18.7%; \( p = 0.01 \); Figure 11). The relative risk of developing deep vein thrombosis with UFH was over two times greater (RR 2.67; CI 95%: 1.18-6.05).

\textit{Figure 11. Incidence of thromboembolic events comparing HIBOR® (Bemiparin) with unfractionated heparin in pre-operative administration\textsuperscript{23}}

<table>
<thead>
<tr>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
</tr>
</tbody>
</table>

- Analysis of the safety parameters

The incidence of intra-operative blood losses, transfusion requirements and haematomas at the injury site did not present any significant difference between the treatment groups.

- Conclusions

A set dose of 3,500 IU of HIBOR® (Bemiparin) administered every 24 hours, with prophylaxis starting 2 hours before surgery, is as effective and safe as UFH in the prevention of DVT in patients subjected to total arthroplasty of the hip. This dosage protocol is of special interest for patients subjected to general anaesthetic.
5.2.2. Thromboembolic prophylaxis starting pre-operatively in orthopaedic surgery

In a prospective, multi-centric, non-randomized pharmacoepidemiological study carried out in a hospital setting in Spain, the effectiveness and tolerability of 3,500 IU of HIBOR® (Bemiparin) was assessed in orthopaedic surgery. To this end, 347 patients were recruited, all underwent arthroplasty of the hip (50.4%) or the knee (49.3%) and with a mean age of 69 ± 8.5 years.

None of the patients treated presented any clinical suspicion of proximal DVT nor of pulmonary embolism. Only 5 cases (1.4%) of thromboembolic complications appeared, all corresponding to distal DVT diagnosed using Doppler ultrasound.

The number of haemorrhagic complications presented during surgery was not high, only 5.2% of patients, with only 0.6% being considered major haemorrhagic complications versus 8.3% reported in the literature.

It can be concluded from this study that 3,500 IU of HIBOR® (Bemiparin) is effective and safe for the prophylactic treatment of VTED in patients subjected to orthopaedic surgery of the hip or knee. In addition to this, there are advantages in its easy administration in a single daily dose and the low incidence of complications, whether haemorrhagic or of any other kind.

5.3 EXTENSION OF THROMBOEMBOLIC PROPHYLAXIS IN ORTHOPAEDIC SURGERY

Normal practice in orthopaedic surgery in recent years has tend to in admitting the patient to hospital for the shortest time possible in order to try to reduce the overall costs. The patient received thromboprophylaxis for an effective time of 7 to 10 days and treatment was suspended on discharge from hospital. In bibliographic reviews41,42, it has been noted that the incidence of recurrence of deep vein thrombosis during the month following surgery is notably reduced if the thromboembolic prophylaxis is continued with LMWHs for a period of 28 to 35 days. Similarly, this extension of prophylaxis has been shown to be profitable in financial terms33.

It has been noted that the incidence of recurrence of deep vein thrombosis is notably reduced if the thromboembolic prophylaxis is continued with LMWHs for a period of 28 to 35 days
5.3.1. Extension of thromboembolic prophylaxis with HIBOR® (Bemiparin)

In the hospital pharmacoepidemiological study into orthopaedic surgery mentioned above, outpatient prophylaxis was continued with HIBOR® after discharge in 237 patients (73%). Of these, 97% received a daily dose of 3,500 IU of HIBOR® (Bemiparin) with a mean duration of prophylactic treatment for 23.8 ± 8 days. An out-patient follow-up was effected 30 days after discharge. During this period only one case of distal DVT was detected.

In this sense, 3,500 IU of HIBOR® (Bemiparin) is available in a presentation containing 30 pre-loaded syringes, with the advantage that a single package provides one month’s thromboprophylactic treatment, covering the recommended period.

5.4 PHARMACOECONOMIC ANALYSIS OF HIBOR® (BEMIPARIN) FOR THROMBOEMBOLIC PROPHYLAXIS IN ORTHOPAEDIC SURGERY

In a multi-centric, non-randomized, prospective, hospital pharmacovigilance study, the efficiency of 3,500 IU of HIBOR® (Bemiparin) was compared with that of different LMWHs (Enoxaparin, Dalteparin, Nadroparin) in the thromboembolic prophylaxis for total or partial hip arthroplasty surgery. Of the 123 patients recruited, 62 followed the treatment with other LMWHs and 61 used a single daily dose of 3,500 IU of HIBOR® (Bemiparin) with prophylaxis starting pre-operatively. The duration of the non-hospital prophylaxis was 21.7 days.

The incidence of VTED episodes did not reveal any differences between the two treatment groups. Nonetheless, the incidence and severity of the complications associated with the treatment were significantly lower in the group receiving 3,500 IU of HIBOR® (Bemiparin), implying a saving in terms of time for dressing injuries and use of medical or surgical materials.

The cost analysis showed that:

- The pharmacological cost of the prophylaxis is significantly lower with 3,500 IU of HIBOR® (Bemiparin) with respect to the group of patients treated with other LMWHs (Figure 12).

- 3,500 IU of HIBOR® (Bemiparin) presents a tendency to have lower costs at different levels of aggregation, with net savings per patient treated of between 78 and 198 euros.

Figure 12. Pharmacological cost of thromboembolic prophylaxis in hip arthroplasty
Mean cost of pharmaceutical treatment (euros)

<table>
<thead>
<tr>
<th>Other LMWHs</th>
<th>HIBOR® (Bemiparin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.001 HIBOR® (Bemiparin) versus other LMWHs</td>
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</tr>
</tbody>
</table>

6. HIBOR® (Bemiparin) for the prophylaxis of thromboembolism in general surgery

6.1 INCIDENCE OF PERI-OPERATIVE THROMBOEMBOLIC DISEASE IN GENERAL SURGERY

The incidence of deep vein thrombosis (DVT) in patients subjected to abdominal surgery when no anti-thrombotic prophylaxis is given is estimated to be between 20% and 30%\(^43\). The incidence of pulmonary embolism (PE) varies between 0.3% and 0.8%\(^43\).

6.2 CLINICAL EXPERIENCE WITH HIBOR® (BEMIPARIN) IN GENERAL SURGERY

6.2.1 Thromboembolic prophylaxis with HIBOR® (Bemiparin) in patients with a low to moderate risk in elective abdominal surgery\(^28\) (comparative study of 2,500 IU of HIBOR® (Bemiparin) versus UFH)

A randomized, prospective, double-blind, multi-centric trial compared the efficacy and safety of 2,500 IU of HIBOR® (Bemiparin), with prophylaxis starting 2 hours pre-operatively and subsequently every 24 hours, against 5,000 IU of UFH subcutaneously every 12 hours. A total of 184 patients of low to moderate risk subjected to elective abdominal surgery were recruited.

In the 166 patients assessed, no cases of DVT, PE or death were noted. The transfusion requirement, subsequent re-operation for haemorrhage and the frequency of haematomas in the injury were significantly lower in the group given 2,500 IU of HIBOR® (Bemiparin) (Figure 13).

\textit{Figure 13. Analysis of the safety parameters in patients with low to moderate risk subjected to elective abdominal surgery}\(^28\)

\begin{tabular}{@{}l@{}c@{}}
\textbf{Patients (%)} & \\
Transfusions (more than 2 units of red globules) & With haematomas at the injury site \\
\end{tabular}

\(*p = 0.035\ \text{HIBOR}®\ (Bemiparin) \text{versus UFH}**p = 0.015\ \text{HIBOR}®\ (Bemiparin) \text{versus UFH}

In conclusion, 2,500 IU of HIBOR® (Bemiparin) is effective and safe in patients with a low to moderate risk of VTED subjected to elective abdominal surgery.
6.2.2 Prophylaxis for thromboembolism with HIBOR® (Bemiparin) in patients with a moderate to high risk in elective abdominal surgery

In a prospective hospital pharmacovigilance study carried out in Spain, the efficacy and safety of HIBOR® (Bemiparin) was assessed in patients with a moderate risk (2,500 IU dose) to high risk (3,500 IU dose) in 203 patients subjected to scheduled surgery of the abdominal wall. The surgical technique most often used was inguinal herniorrhaphy (59.1%). The initial dose was administered two hours prior to the intervention and prophylaxis was subsequently maintained for an average of 2.52 ± 2 days.

Among the 203 patients, only 2 episodes of thromboembolism occurred (1.2%), one distal DVT and one case of pulmonary embolism, although neither of these causes led to death. There were no complications related to the treatment in 77.8% of patients and, when these appeared, they were mostly of little importance: haematoma at the surgical site of injury (6.9%), ecchymosis at the injection site (9.9%). Only 2 cases of major bleeding were described (1.0%), together with 4 cases of intra-operative haemorrhage (2.0%). No patient required transfusion of haemoderivatives nor were significant differences observed in the analytical parameters. No cases of thrombopenia or allergic reaction occurred related to the treatment.

In conclusion, HIBOR® (Bemiparin) is effective and safe in the prophylaxis of thromboembolism in patients subjected to abdominal surgery with a moderate to high risk of VTED.

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HIBOR®, 3,500 IU, is effective and safe in the prophylaxis of thromboembolism in patients subjected to abdominal surgery with a moderate to high risk of VTED

6.2.3 Prophylaxis of thromboembolism with HIBOR® (Bemiparin) in oncological surgery

Abdominal or pelvic surgery in patients with cancer has a high risk of developing VTED.

It has recently been shown in a trial conducted with this type of patient that the continuation of the prophylactic treatment for DVT with LMWHs for 4 weeks is more effective than the normal clinical pattern of one week’s treatment.

On the other hand, a retrospective register\textsuperscript{45} of 197 patients subjected to oncological, mainly abdominal surgery, who received post-operative prophylaxis with HIBOR\textsuperscript{®} (Bemiparin), only 4 presented episodes of thromboembolism (2\%). This seems to confirm the effectiveness of HIBOR\textsuperscript{®} (Bemiparin) also in this population with a high risk of suffering VTED.
7. HIBOR® (Bemiparin) in the primary prophylaxis for thromboembolism in non-surgical patients

7.1 VTED RISK FACTORS IN NON-SURGICAL PATIENTS

Two out of three patients with DVT do not have a history of recent surgery and, therefore, primary prophylaxis for VTED must not focus exclusively on surgical patients. Patients with stroke or cardiovascular events, those over 60 years of age with heart failure or shock, or even patients with a history of VTED or congenital thrombophilia are considered to be at high risk (Table VII). Prophylaxis with LMWHs is recommended in medical patients with VTED risk factors (including cancer, being bedridden, severe pulmonary disease, heart failure).

Table VII. Stratification of the risk in non-surgical patients

<table>
<thead>
<tr>
<th>High risk</th>
<th>Moderate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Patient immobilized with an active disease</td>
<td>Minor medical disease</td>
</tr>
<tr>
<td>Heart failure in those over the age of sixty</td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of VTED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophilia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.2 CLINICAL EXPERIENCE WITH HIBOR® (BEMIPARIN) IN NON-SURGICAL PATIENTS

In order to assess the efficacy and safety profile of HIBOR® (Bemiparin) in non-surgical patients with a moderate to high risk of suffering VTED, a prospective hospital pharmacovigilance study was carried out under conditions of real clinical practice, with the inclusion of 297 patients from Internal Medicine and other medical specialities in 13 centres in Spain.

Primary prophylaxis for VTED must not focus exclusively on surgical patients

If the risk was moderate, 2,500 IU of HIBOR® (Bemiparin) were administered subcutaneously and 3,500 IU of HIBOR® (Bemiparin) if the risk was high, both in a single daily dose. Prophylaxis was maintained at the physician’s discretion during the period of risk or until the complete mobilization of the patient, even after
hospital discharge if necessary. The mean age of the patients included was 75 years (range 31-98). The most frequent reason for admission to hospital was cardiac pathology (31.7%), followed by lung disease (21.4%) and infection diseases (19.9%). The VTED risk factors most commonly founded included the elderly age of the patients (97.3%), immobilization (80.5%) and heart failure (41.1%).

**HIBOR® presents an adequate effectiveness in non-surgical patients with a moderate to high risk of VTED**

During admission, only one case of thromboembolic complication arose in one patient (0.3%), corresponding to a case of pulmonary embolism diagnosed by means of scintigraphy. Most patients in the study (80.8%) did not present any complication due to the prophylactic treatment. In the remainder, most of the complications were minor, being a small ecchymosis at the site of the injection the one most commonly referred (14.3%). There were 9 cases (3%) of major bleeding, most of digestive origin and in patients associating multiple pathologies. Only in 2 patients (0.7%) presented an allergic reaction and thrombopenia associated with the treatment.

In conclusion, **HIBOR®** (Bemiparin) presents an adequate level of effectiveness in non-surgical patients with a moderate to high risk of VTED.
8. HIBOR® (Bemiparin) in the treatment of established venous thromboembolic disease

8.1 GOALS OF THE TREATMENT OF ESTABLISHED VENOUS THROMBOEMBOLIC DISEASE

Thromboembolic disease requires appropriate treatment in its acute phase to prevent death by pulmonary embolism. A long-term extension of the treatment is required in many cases to prevent later relapses\(^{47}\).

The main objectives of the short-term treatment are the prevention of the spread of the thrombus and potentially fatal pulmonary embolization, as well as the onset of recurrent episodes of VTED\(^{47}\).

In the long term, the purpose of the treatment is to prevent late relapses and sequelae such as post-phlebitic syndrome and pulmonary hypertension\(^ {47}\).

The Deep Vein Thrombosis Treatment study (the DVTT study) has proved the efficacy and safety of HIBOR\(^ {®}\) in the acute treatment of established DVT, with or without pulmonary embolism, and the subsequent prevention of secondary recurrences.

Several randomized controlled trials have shown that LMWHs are at least as safe and effective as UFH in the treatment of the acute phase of DVT\(^ {47}\). Other trials have compared the LMWHs and oral anti-coagulants in the prevention of recurrences of DVT\(^ {48-52}\).

The Deep Vein Thrombosis Treatment study\(^ {24-26}\) (the DVTT study) has proved the efficacy and safety of HIBOR\(^ {®}\) (Bemiparin) in the acute treatment of established DVT, with or without pulmonary embolism, and the subsequent prevention of secondary recurrences.

8.2 DESIGN OF THE DVTT STUDY\(^ {24-26}\)

In this randomized, open-label multi-centric trial with parallel groups and masking of the assessment of the results, a total of 378 patients with symptomatic acute DVT (over the age of 18 years) were distributed into three treatment groups (Figure 14):
**Group A**: treatment for 7 ± 2 days with UFH followed by long-term treatment with Warfarin.

**Group B**: treatment for 7 ± 2 days with 115 IU/kg/day of HIBOR® (Bemiparin) subcutaneously followed by long-term treatment with Warfarin.

**Group C**: treatment for 10 days with 115 IU/kg/day of HIBOR® (Bemiparin) subcutaneously followed by long-term treatment with HIBOR® (Bemiparin) at a fixed daily dose of 3,500 IU subcutaneously.

*Figure 14. Design of the DVTT study*
HIBOR (Bemiparin): 5,000 IU/day (weight: < 50 kg); 7,500 IU/day (weight: 50-70 kg); 10,000 IU/day (weight: > 70 kg)

Fifty-four patients were excluded from the intention to treat analysis: 6 of them had not a baseline phlebography and in the other 48 DVT was not confirmed in the initial phlebography. Thus, the remaining 324 patients make up the intention-to-treat group and 27 of these were not included in the protocol analysis as the phlebography on the 14th day was not performed.

8.3 EFFICACY OF HIBOR® (BEMIPARIN) IN THE ACUTE TREATMENT OF ESTABLISHED VTED IN COMPARISON WITH UFH

During acute treatment, the main efficacy variable was the variation in the size of the thrombus (as determined by phlebography) between the first and the 14th day (± 2 days), assessed in accordance with the Marder index. According to this index, a score is assigned to the affected deep vein system in the lower limbs. If all of the veins in the limb are obstructed by thrombi, the score will reach 40 (6 for the iliac vein, 4 for the ordinary femoral, 10 for the surface femoral, 4 for the popliteal, 4 for the anterior tibial and 6 for the posterior tibial). The veins with partial occlusion are given a lower score depending on the magnitude of the thrombus. A certain correlation has been described between the clinical evolution and the variation in the size of the thrombus as measured by the Marder index. The phlebograms were assessed by two members of an independent committee who were not aware of the treatment assigned to each patient.

Treatment with 115 IU/kg/day of HIBOR® subcutaneously is significantly more effective in the regression of thrombi and at least as safe and effective as treatment with UFH in acute VTED from the clinical standpoint.

Figure 15. Reduction in the size of the thrombus between day 1 and day 14 of the trial. Assessed using the Marder index.

Patients with improvement according to the Marder index (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH (7 ± 2 days)</td>
<td>n = 98</td>
<td></td>
</tr>
<tr>
<td>HIBOR® (Bemiparin)</td>
<td>n = 105</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115 IU/kg/day (7±2 days)</td>
<td></td>
</tr>
<tr>
<td>HIBOR® (Bemiparin)</td>
<td>n = 94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115 IU/kg/day (10 days)</td>
<td></td>
</tr>
</tbody>
</table>

*p=0.004 Hibor® (Bemiparina) vs UFH

**p=0.005 Hibor® (Bemiparina) vs UFH
Patients were classified into two groups: “with improvement” and “without improvement” according to the Marder index between day 1 and day 14. The proportion of patients with improvement was 52% in group A (51/98), 72% in group B (76/105) and 72% in group C (68/94) (Figure 15). The degree of improvement in group B in excess of 20% indicates the non-inferiority of HIBOR® (Bemiparin) (p = 0.00003) and also its superiority (p = 0.004) versus UFH. The same result was obtained when groups A and C are compared (non-inferiority p = 0.0005; superiority p = 0.005)²⁵,²⁶.

In conclusion, 115 IU/kg/day of HIBOR® (Bemiparin) subcutaneously is significantly more effective in the regression of thrombi and at least as safe and effective from the clinical standpoint as treatment with UFH in acute VTED²⁶.

8.4 EFFICACY OF 3,500 UI OF HIBOR® (BEMIPARIN) COMPARED WITH ORAL ANTI-COAGULANTS IN THE PREVENTION OF VTED RECURRENCES

The second phase of the DVTT Study²⁴,²⁵ assessed the feasibility of preventing recurrences of DVT for three months with 3,500 UI of HIBOR® (Bemiparin) as an alternative treatment to oral anti-coagulants. This trial used Warfarin as the oral anti-coagulant because this is the drug of choice in most countries participating in the trial. The recanalization of the veins affected was measured by means of phlebography or Doppler ultrasound on the 84th day of the study. Patients were classified according to their total or partial recanalization or by the absence of improvement.

Figure 16. Recanalization index of the deep veins affected, on the 84th day of the study, measured by phlebography or Doppler ultrasound

<table>
<thead>
<tr>
<th>Patients with recanalization (%)</th>
<th>Warfarin (Prior treatment with UFH) n=85</th>
<th>Warfarin (Prior treatment with Bemiparin) n=89</th>
<th>HIBOR® (Bemiparin) 3,500 IU/day sc (Prior treatment with Bemiparin) n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial recanalization</td>
<td></td>
<td>Total recanalization</td>
<td></td>
</tr>
</tbody>
</table>
The protocol population for this long-term stage of the trial comprised 255 patients. The total or partial recanalization rate did not show significant differences between the groups (Figure 16) and was 75.3% (64/85) in group A, 79.8% (71/89) in group B and 81.5% (66/81) in group C.

The incidence of recurrent thromboembolic events between day 1 and day 84 of treatment did not reach statistically significant differences between the groups (3.63% in group A, 0.9% in group B and 2.91% in group C).

**Unlike oral anti-coagulants, treatment with 3,500 IU of HIBOR® (Bemiparin) does not require regular coagulation tests to be made**

Thus, when 3,500 IU of HIBOR® (Bemiparin) is administered long-term, it is as effective as the oral anti-coagulants in the prevention of recurrences of venous thromboembolism over three months. In addition, 3,500 IU of HIBOR® (Bemiparin) may represent a safe, effective and convenient alternative to oral anti-coagulants. This new alternative is interesting, particularly in patients at risk of bleeding or in those where oral anti-coagulants are contraindicated.

Although the price is higher than that of the oral anti-coagulants, the cost analyses indicate that it is profitable for the health-care system, as the length of the hospital stay of the patients treated with LMWHs is shortened by an average of 3 days. The savings may be even greater since, unlike oral anti-coagulants, treatment with 3,500 IU of HIBOR® (Bemiparin) does not require regular coagulation tests to be made.

**8.5 SAFETY OF HIBOR® (BEMIPARIN) IN THE ACUTE AND LONG-TERM TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE**

The main safety variables in the DVTT study were haemorrhagic complications, classified as mild or severe. The frequency of this type of complications was similar in the three groups (Figure 17). The frequency of adverse events, mortality and heparin-induced thrombocytopenia did not vary among different study groups during the short and long-term treatments.

*Figure 17. Incidence of major and minor haemorrhage between day 1 and day 84.*

Incidence of major and minor haemorrhage (%)
9. HIBOR® (Bemiparin) in the prevention of coagulation in the extracorporeal flow circuit during haemodialysis

The surfaces of the extracorporeal circuit constitute a stimulus for the activation of coagulation and the generation of fibrin. As a result of the total or partial obstruction of the flow, the efficacy of the filtering may be hindered or even become impossible55.

In order to verify the safety and efficacy of HIBOR® (Bemiparin) in preventing the clotting of haemodialysis circuits (HD), a clinical trial55 was conducted in two centres recruiting patients of both sexes over the age of 18 with stable chronic renal failure regardless of aetiology, scheduled for haemodialysis for a period longer than 6 months. A total of 67 patients were included, with a total of 2,671 haemodialysis sessions being conducted, 1,426 of them with HIBOR® (Bemiparin) and 1,245 with UFH.

The goal of this clinical trial, on the one hand, was to confirm the dosage necessary to prevent coagulation in the haemodialysis sessions and, secondly, to assess the efficacy of the dialysis lines or devices in terms of the appearance of thromboses.

HIBOR® (Bemiparin) can be used safely and effectively for the prevention of clotting in the extracorporeal flow circuit during haemodialysis

Another objective proposed was the assessment of the safety of HIBOR® (Bemiparin) in terms of the appearance of haemorrhagic accidents, particularly the bleeding time of the arteriovenous fistula (AVF) once haemodialysis is concluded.

The doses required for haemodialysis were established by applying a multivariate linear model, including the following variables: inverse of the dose in IU of anti-FXa/kg, weight of the patient in kg and plasma levels of anti-FXa activity in IU/ml. The resulting equation was

$$\frac{1}{\text{dose}} = 0.031 + 0.00013 \text{ weight} - 0.018 \text{ anti-FXa}$$

From the application of this equation, it was concluded that the doses to be administered would be:

- 2,500 UI of HIBOR® (Bemiparin) for the patients weighing 60 kg or less.
- 3,500 UI of HIBOR® (Bemiparin) in subjects weighing more than 60 kg.
With regard to the coagulation of the dialysis device or in the haemodialysis circuits, no cases of complete clotting were observed in the dialysis device or lines. A certain deposit of fibrin in the device or the presence of clots in the bubble trap could be seen in 70 dialysis sessions (6.2%), of which half presented plasma levels at the end of HD of less than 0.4 IU/ml and the other half between 0.4 and 0.8 IU/ml. Nonetheless, although a discreet but significant increase was observed in the percentage of coagulation in the dialysis device, no differences were detected between HIBOR® (Bemiparin) and UFH.

No severe haemorrhagic complications were observed in any of the patients under study. Furthermore, the bleeding of the fistula, considered as a safety variable, was similar to that with UFH or HIBOR® (Bemiparin), although the time for closure of the fistula was a little shorter with HIBOR® (Bemiparin) (Figure 18).

*Figure 18. Time for closure of the arteriovenous fistula after completion of the haemodialysis session*

<table>
<thead>
<tr>
<th>HD sessions (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 minutes</td>
<td>&gt; 10 minutes</td>
</tr>
</tbody>
</table>

In summary, we can conclude that HIBOR® (Bemiparin) can be used safely and effectively for the prevention of clotting in the extracorporeal flow circuit by administering a single dose of 2,500 IU (for patients weighing 60 kg or less) or 3,500 UI (in those weighing more), in the form of a bolus in the arterial line of the dialysis circuit at the start of the session.
10. Other areas of clinical investigation

ROVI, S.A. Pharmaceutical Laboratories are currently undertaking further studies with HIBOR® (Bemiparin) not only to increase the information available on the populations of patients with the greatest risk of suffering VTED but also in new lines of clinical investigation.

Very recently, a study\textsuperscript{56} has just been published with HIBOR® (Bemiparin) in patients with congestive heart failure (CHF) and the most noteworthy aspects of this trial are indicated below.

10.1 HIBOR® (BEMIPARIN) IN CONGESTIVE HEART FAILURE

CHF is associated with an increased risk of arterial thrombosis and VTED, regardless of whether or not it is associated with auricular fibrillation\textsuperscript{57}. It is well-known that CHF is associated with a state of hypercoagulability, with high plasma levels of various factors and complexes which impact this prothrombotic state\textsuperscript{58}.

For this reason, it was proposed to carry out a double-blind, placebo-controlled trial in patients with hypercoagulability, such as CHF, so as to demonstrate the potential beneficial effects of HIBOR® (Bemiparin) on various parameters reflecting a reduction in thrombin and plasmin\textsuperscript{56}.

A total of 100 patients with CHF grade NYHA II to IV and who had received 3,500 UI/day of HIBOR® (Bemiparin) or placebo for 5-10 days (median 5 days in both groups) were recruited. The haemostatic parameters were measured for baseline values, after 24 hours and on discharge from hospital (from 4 to 10 days after the random allocation to treatment). No significant differences were found between the two groups at the baseline visit. In the group treated with HIBOR® (Bemiparin), after 24 hours and on discharge, a significant increase was observed in protein C (PC) and significant reductions in D-dimer, prothrombin fragments 1 and 2 (PF1+2), factor VII:c and thrombin anti-thrombin complex (TAT), whereas in the group receiving placebo, they found a significant reduction in PC and significant increases in the other haemostatic parameters (Tables VIII and IX)\textsuperscript{56}. 
Table VIII. Changes in haemostatic parameters at 24 hours respect to baseline values\textsuperscript{56}

<table>
<thead>
<tr>
<th></th>
<th>HIBOR\textsuperscript{®} (Bemiparin) 3,500 IU/day</th>
<th>Placebo</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (%)</td>
<td>+3.5</td>
<td>-4.0</td>
<td>0.01</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>-14.0</td>
<td>+24.3</td>
<td>0.009</td>
</tr>
<tr>
<td>PF1+2 (nmol/l)</td>
<td>-0.11</td>
<td>+0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>F VII:c (%)</td>
<td>-1.7</td>
<td>0.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\*HIBOR\textsuperscript{®} (Bemiparin) 3,500 IU/day vs. placebo

Thus, this trial shows that therapy with HIBOR\textsuperscript{®} (Bemiparin) may modify the hypercoagulability markers in patients with heart failure. If the hypercoagulability status is taken as a marker for the clinical events in heart failure, then the anticoagulation treatment should offer benefits for these patients\textsuperscript{56}.

\textbf{HIBOR\textsuperscript{®} may modify the hypercoagulability markers in patients with congestive heart failure}

Table IX. Changes in haemostatic parameters\textsuperscript{56} on discharge from hospital (after 4 to 10 days of treatment) with respect to the baseline values

<table>
<thead>
<tr>
<th></th>
<th>HIBOR\textsuperscript{®} (Bemiparin) 3,500 IU/day</th>
<th>Placebo</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (%)</td>
<td>+16.0</td>
<td>+0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>-44.0</td>
<td>+3.8</td>
<td>0.002</td>
</tr>
<tr>
<td>TAT complex (µg/dl)</td>
<td>-0.7</td>
<td>+0.14</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* 3,500 IU/day of HIBOR\textsuperscript{®} (Bemiparin) versus placebo
11. Indications and presentations

11.1 INDICATIONS

**HIBOR® 2,500 IU – HIBOR® 3,500 IU**

- Prophylaxis of thromboembolic disease in patients subjected to general and orthopaedic surgery
- Prophylaxis of thromboembolic disease in non-surgical patients with moderate or high risk
- Prophylaxis of coagulation in the extracorporeal flow circuit during haemodialysis

**HIBOR® 3,500 IU**

- Secondary prevention of recurrence of venous thromboembolism in patients with deep vein thrombosis and transient risk factors

**HIBOR® 5,000 IU – HIBOR® 7,500 IU – HIBOR® 10,000 IU**

- Treatment of established deep vein thrombosis, with or without pulmonary embolism

11.2 PRESENTATIONS

**HIBOR® 2,500 IU**

- 2 pre-loaded syringes
- 10 pre-loaded syringes
- 100 pre-loaded syringes (clinical pack)

**HIBOR® 3,500 IU**

- 2 pre-loaded syringes
- 10 pre-loaded syringes
- 30 pre-loaded syringes
- 100 pre-loaded syringes (clinical pack)
HIBOR® 5,000 IU
- 2 pre-loaded syringes
- 10 pre-loaded syringes
- 30 pre-loaded syringes
- 100 pre-loaded syringes (clinical pack)

HIBOR® 7,500 IU
- 2 pre-loaded syringes
- 10 pre-loaded syringes
- 30 pre-loaded syringes
- 100 pre-loaded syringes (clinical pack)

HIBOR® 10,000 IU
- 2 pre-loaded syringes
- 10 pre-loaded syringes
- 30 pre-loaded syringes
- 100 pre-loaded syringes (clinical pack)


molecular weight heparin (RO-11) - a three way cross-over study in healthy volunteers. Thromb Res 1995;78(1):77-86.


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40. Circular 10/2001 de la Agencia Española del Medicamento. BOE 05/11/01 (20607).


45. Datos de archivo ROVI S.A. (available).


13. Glossary of abbreviations

**AEM**: Spanish Medicines Agency

**aPTT**: (activated) partial thromboplastin time

**AVF**: arteriovenous fistula

**CHF**: congestive heart failure

**CI**: confidence interval

**D**: Daltons

**DVT**: deep vein thrombosis

**DVTT**: deep vein thrombosis treatment

**FDA**: Food and Drug Administration

**FIIa**: factor IIa

**FXa**: factor Xa

**HD**: haemodialysis

**ITT**: intention to treat population

**IU**: international units

**iv**: intravenous

**LMWH**: low molecular weight heparin

**MW**: molecular weight

**PC**: protein C

**PE**: Pulmonary embolism

**PP**: per protocol population

**RR**: relative risk

**sc**: subcutaneous

**TAT**: thrombin anti-thrombin complex

**TF**: tissue factor

**TFPI**: plasma tissue factor pathway inhibitor

**UFH**: unfractionated heparin

**VTED**: venous thromboembolic disease