COMPANY CORE DATA SHEET – CCDS (EDS/CORE/ENGLISH)

BERININ® P 300/600/1200

Rev.: 13-NOV-2009 / Mix2Vial 1-carton version

Supersedes previous versions
Rev.: 07-DEC-2007 / PEI approval 07.12.07
Rev.: 30-NOV-2007 / PEI comments 27.11.07
1. TRADE NAME OF THE MEDICINAL PRODUCT

Berinin® P 300/600/1200
Powder and solvent for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Berinin P is presented as a powder and solvent for solution for injection or infusion containing nominally 300 IU, 600 IU or 1200 IU human coagulation factor IX per vial.

After reconstitution with 2.5 ml, 5 ml and 10 ml respectively of water for injections the product contains approximately 120 IU/ml (300 IU/2.5 ml, 600 IU/5 ml, 1200 IU/10 ml) human coagulation factor IX.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Berinin P is at least 50 IU factor IX mg total protein.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

*Posology*

The dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency on the location and extent of the bleeding and on the patient's clinical condition.
The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an international standard for factor IX in plasma). One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

The calculation of the required dosage of factor IX is based on the empirical finding that International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1.0% of normal activity.

The required dosage is determined using the following formula:

Required units = body weight [kg] x desired factor IX rise [% or IU/dl] x 1.0*.

The amount to be administered and the frequency and duration of administration should always be oriented towards the clinical efficacy in the individual case. Factor IX products rarely require to be administered more than once daily.

* reciprocal of observed recovery
In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

<table>
<thead>
<tr>
<th>Degree of haemorrhage/ Type of surgical procedure</th>
<th>Factor IX level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat infusion every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages:</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30-60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major 80-100 (pre- and postoperative)</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% - 60% (IU/dl).</td>
<td></td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of in vivo recovery and demonstrating different half-lives.

For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kg of body weight at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.
Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia. See also section 4.4.

**Dosage in children**
No data from clinical trials regarding the dosage of Berinin P in children are available.

**Method of Administration**

Reconstitute the product as described at section 6.6.

The reconstituted preparation should be warmed to room or body temperature before administration. Inject or infuse slowly intravenously at a rate which the patient finds comfortable. Take care to ensure that no blood enters the syringe filled with product. The injection or infusion rate should not exceed 2 ml per minute.

Observe the patient for any immediate reaction. If any reaction takes place that might be related to the administration of Berinin P, the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient (see also section 4.4).

**4.3 Contra-indications**

Known hypersensitivity to any of the constituents of the preparation.

**4.4 Special warnings and special precautions for use**

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

In case of shock, the current medical standards for shock treatment should be observed.

After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.
There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX concentrates, the initial administrations of factor IX should, according to the treating physician’s judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC). Because of the potential risk of thromboembolic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with Berinin P should be weighed against the risk of these complications.

Berinin P contains up to 48 mg sodium per 1200 IU. To be taken into consideration by patients on a controlled sodium diet.

Berinin P contains heparin as excipient. Heparin may cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.

**Virus safety**
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV.

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and hepatitis B) should be generally considered for patients in regular/repeated receipt of human plasma-derived Factor IX products.

It is strongly recommended that every time that Berinin P is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interactions with other medicinal products and other forms of interactions

No interactions of human plasma coagulation factor IX products with other medicinal products are known.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with factor IX.

Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available.

Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The following adverse reactions base on postmarketing experience. The following standard categories of frequency are used:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>&gt; 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>1/100 and &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1/1,000 and &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>1/10,000 and &lt;1/100</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000 (including reported single cases)</td>
</tr>
</tbody>
</table>

**Immune system disorders:**

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed very rarely in patients treated with factor IX containing
products. In very rare cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also 4.4).

Patients with haemophilia B may very rarely develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is very limited experience with Berinin P from clinical studies in previously untreated patients (PUPs). Therefore, no valid data about the incidence of clinically relevant, specific inhibitors can be given.

**General disorders and administration site conditions:**
On very rare occasions, fever has been observed.

**Renal and urinary disorders:**
There is one report available describing the occurrence of nephrotic syndrome following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

**Vascular disorders:**
In very rare cases there is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such side effects.

**Blood and lymphatic system disorders:**
Very rare cases have been reported in which patients have developed a heparin-associated thrombocytopenia (HAT Type II), with the platelets dropping distinctly below 100,000 per µl or to less than 50 % of their baseline value. In patients without preexisting hypersensitivity to heparin the fall in the platelet count generally commences 6 to 14 days after the start of treatment. In patients hypersensitive to heparin this fall may occur within hours.

The severe form of thrombocytopenia may be associated with arterial and venous thromboses/thrombembolisms, consumption coagulopathy, in some cases with cutaneous necroses at the site of injection, petechiae, purpura and melaena. In these cases the inhibitory effect of heparin on blood coagulation may be diminished (heparin tolerance).

Berinin P must be discontinued immediately in patients who develop the aforementioned allergic reactions. These patients have to be informed that they also must not receive any heparin-containing drugs at any future time.

For information on viral safety see 4.4.
4.9 Overdose

No symptoms of overdose with human coagulation factor IX have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group:
Antihaemorrhagics/Blood coagulation factor IX.
ATC code: B02B D04

Factor IX is a single chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin K-dependent coagulation factor and is synthesized in the liver. Factor IX is activated by factor Xla in the intrinsic coagulation pathway and by the factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X.

Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen to fibrin and a clot is formed. Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

5.2 Pharmacokinetic properties

In a pharmacokinetic study with 14 patients the median half-life was 23 hours (10 – 43 hours), the median IVR 1.1 (IU/dl)/(IU/kg) (0.57 – 1.69 (IU/dl)/(IU/kg)). The median MRT was 27 hours (18 – 40 hours) and the median clearance was calculated with 4.5 ml/h/kg (2.5 – 12.5 ml/h/kg).

5.3 Preclinical safety data

Berinin P contains factor IX as active ingredient which is derived from human plasma and acts like the endogenous constituent of plasma. Single dose applications of Berinin P to various animal species did not reveal toxic effects. Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity, reproductive toxicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aminoacetic acid, antithrombin III, calcium chloride, heparin, sodium chloride, sodium citrate, HCl or NaOH (in small amounts for pH adjustment).

Supplied solvent:
Water for injections 2.5/5/10 ml

6.2 Incompatibilities

Berinin P must not be mixed with other medicinal products, diluents or solvents.

6.3 Shelf life

3 years.

After reconstitution the physico-chemical stability has been demonstrated for 16 hours at room temperature (max. +25 °C). From a microbiological point of view and as Berinin P contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours at room temperature.

6.4 Special precautions for storage

Berinin P is to be stored at +2 to +25 °C. Do not freeze.

Keep vial in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Immediate containers

Substance vials:

Berinin P 300 IU:
– Injection vial of 6 ml, colourless, glass type I Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.

Berinin P 600 IU
– Injection vial of 10 ml, colourless, glass type I Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.
Berinin P 1200 IU:
- Injection vial of 17 ml, colourless, glass type II Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.

**Diluent vials (for water for injections):**

2.5 ml for Berinin P 300 IU:
- Injection vial of 6 ml, colourless, glass type I Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.

5 ml for Berinin P 600 IU:
- Injection vial of 6 ml, colourless, glass type I Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.

10 ml for Berinin P 1200 IU:
- Injection vial of 10 ml, colourless, glass type I Ph. Eur., sealed with rubber stopper (latex free) and aluminium-polypropylene crimp cap.

**Presentations**

*Berinin P 300:*
1 vacuum vial with powder
1 vial with 2.5 ml water for injections
1 filter transfer device 20/20

*Berinin P 600:*
1 vacuum vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20

*Berinin P 1200:*
1 vacuum vial with powder
1 vial with 10 ml water for injections
1 filter transfer device 20/20

Not all pack sizes may be marketed.

### 6.6 Instructions for use/handling

**General instructions**
- Berinin P must not be used after the expiry date given on the pack and container.
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or contain residues (deposits/particles).
- Reconstitution and withdrawal must be carried out under aseptic conditions.
- Any unused product or waste material should be disposed of in accordance with local requirements.

**Reconstitution:**
Bring the solvent to room temperature. Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Open the Mix2Vial package by peeling away the lid.</td>
</tr>
<tr>
<td>2</td>
<td>Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the package and snap the blue end onto the diluent stopper.</td>
</tr>
<tr>
<td>3</td>
<td>Carefully remove the package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set.</td>
</tr>
<tr>
<td>4</td>
<td>With the product vial firmly on a surface, invert the diluent vial with set attached and snap the transparent adapter onto the product vial stopper. The diluent will automatically transfer into the product vial.</td>
</tr>
<tr>
<td>5</td>
<td>With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved. Do not shake the vial.</td>
</tr>
</tbody>
</table>
6. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the diluent-side of the Mix2Vial set and unscrew the set into two pieces. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial set. Inject air into the product vial.

<table>
<thead>
<tr>
<th>Withdrawal and application:</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.</td>
</tr>
<tr>
<td>8. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the Mix2Vial set from the syringe.</td>
</tr>
</tbody>
</table>

For injection of Berinin P the use of plastic disposable syringes is recommended as the ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

7. MARKETING AUTHORIZATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. MARKETING AUTHORIZATION NUMBER(S)

- country specific -
9. DATE OF THE AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

- country specific -

10. DATE OF (PARTIAL) REVISION OF THE TEXT

November 2009