SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BETAFACT 50 IU/ml, powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human coagulation factor IX .....50 IU*/ml
in reconstituted solution

Once reconstituted with 5, 10 or 20 ml of water for injections, one vial contains 250 IU/5 ml, 500 IU/10 ml, 1000 IU/20 ml of human coagulation factor IX.

* The potency (IU) is determined using the European Pharmacopeia one-stage clotting test against the World Health Organization (OMS) International standard (WHO 84/683).

The specific activity of human coagulation factor IX is approximately 110 IU/mg protein.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Human coagulation factor IX is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

4.2. Posology and method of administration

Posology

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

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.

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 human coagulation factor IX 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 1 International Unit (IU) of human coagulation factor IX per kg body weight raises the plasma factor IX activity by 1.08 % of normal activity. The required dosage is determined using the following formula:

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor IX rise (\%) (IU/dl)} \times 0.93$$

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Human coagulation factor IX products rarely require to be administered more than once daily.

In case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

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

Under certain circumstances larger doses than those calculated may be required, especially for the initial injection.

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 injections. In case of major surgical interventions in particular, precise monitoring of the substitution 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 human coagulation factor IX per kilogram 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. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml increase of the dose of human coagulation factor IX may suffice to neutralise the inhibitors. In patients with inhibitor above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (aPCC) or activated factor VII (FVIIa) has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

In clinical trials, 11 children less than 6 years old have been treated with BETAFACT at a posology identical to that used in adults, but adjusted for their body weight (see also 4.4 "Special warnings and special precautions for use").

Method of administration

Reconstitute the preparation as described at 6.6 "Instructions for use, handling and disposal". The product should be administered via the intravenous route.

It is recommended that human coagulation factor IX should not be administered at a flow rate in excess of 4 ml/minute.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and special precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. The product contains traces of human proteins other than factor IX.

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.

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. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia).

Appropriate vaccination (hepatitis A and hepatitis B) for patients in receipt of plasma derived factor IX concentrates is recommended.

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 human coagulation 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.

The product should be used with caution in children less than 6 years, who have limited exposure to factor IX products.
The product should be used with caution in previously untreated patients for whom clinical experience is limited.

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 thrombotic 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 human coagulation factor IX should be weighed against the risk of these complications.

4.5. Interaction with other medicinal products and other forms of interaction

No interactions of human 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 breast-feeding is not available. Therefore, factor IX shoul 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

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently in patients treated with human coagulation factor IX containing products. In some 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 "Special warnings and special precautions for use"). The treatment required depends on the nature and severity of the reaction.

Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors.

On rare occasions, fever has been observed.

Patients with haemophilia B may 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.

No inhibitor has been detected during the BETAFACT clinical studies in 11 previously untreated patients.

There is a potential risk of thrombo-embolic 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 highly purified human coagulation factor IX such as BETAFACT is rarely associated with such side effects.

For safety with respect to transmissible agents, see 4.4.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Antihemorrhagics: blood coagulation factor IX.
ATC code: B02BD04

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 it is synthesised in the liver. Factor IX is activated by factor XIa 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 into 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 level of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

5.2. Pharmacokinetic properties

The plasma peak of human coagulation factor IX usually occurs between 15 and 30 minutes after injection.

Recovery is 1.08 ± 0.21 IU/dl/IU/kg.

The area under the curve is equivalent to 1888 ± 387 IU.h/dl. The mean residence time is 44.2 ± 4.9 h.

The half-life of BETAFACT is 33 ± 4 hours.

The clearance of the active substance FIX:C is 3.3 ± 0.5ml/h/kg.

5.3. Preclinical safety data

The factor IX contained in this preparation is a normal constituent of human plasma and behaves in the same manner as endogenous factor IX.

No reproduction studies have been performed in animals.

The available preclinical data (Ames test) do not suggest any mutagenic effects from human coagulation factor IX. A local tolerability study in rabbits demonstrated that human coagulation factor IX was well tolerated using an intravenous administration and even tolerated in the case of an accidental peri-venous or intra-arterial administration.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder: sodium chloride, sodium heparin, lysine hydrochloride, arginine, sodium citrate.
Solvent: water for injections.

6.2. Incompatibilities

This medicinal product must not be mixed with any other substance or medicinal products.
Only polypropylene injection/infusion sets can be used because treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some infusion equipment.

6.3. Shelf life

In its original package: 30 months.
Reconstituted solution: the product should be used immediately (although it has been shown to be stable for 3 hours at +25°C).

6.4. Special precautions for storage

Store in a refrigerator (+2°C - +8°C).
The product may be stored within its shelf-life at a temperature not exceeding 25°C for a maximum of 6 months, without being "re-refrigerated" during this period. It must be discarded if it is not used within this 6-month period.
Do not freeze.
Keep the container in the outer carton in order to protect from light.

6.5. Nature and contents of container

Powder in a vial (glass type I) + 5 ml of solvent in a vial (glass type II) with a transfer system and a filter needle - box of 1.

Powder in a vial (glass type I) + 10 ml of solvent in a vial (glass type II) with a transfer system and a filter needle - box of 1.

Powder in a vial (glass type I) + 20 ml of solvent in a vial (glass type II) with a transfer system and a filter needle - box of 1.

6.6. Instructions for use, handling and disposal

Do not use after the expiry date given on the label.

Reconstitution:

Use current guidelines for aseptic procedure.

- If necessary, bring the two vials (powder and solvent) to ambient temperature.
- Remove the protective cap from the solvent vial (water for injections) and from the powder vial.
- Disinfect the surface of each stopper.
- Remove the translucent protective sheath from the transfer system and completely insert the exposed needle through the centre of the stopper of the solvent vial while simultaneously twisting the needle.
- Remove the second protective sheath from the other end of the transfer system.
- Keeping both vials horizontal (vented spike pointing upwards), quickly push the free end of the needle into the centre of the stopper of the powder vial.
  Ensure that the needle always remains immersed in the solvent to avoid releasing the vacuum prematurely.
- Immediately place the system upright in a vertical position, keeping the solvent vial directly above the powder vial, to allow the solvent to transfer into the powder.
- During the transfer, direct the jet of solvent over the whole surface of the powder. Ensure that all of the solvent is transferred.
- The vacuum is automatically released at the end of the transfer procedure (sterile air).
- Remove the empty vial (solvent) with the transfer system.
- Gently swirl for a few minutes with a rotating movement to avoid the formation of foam until the powder has completely dissolved.
- The powder generally dissolves instantaneously and should be completely dissolved in less than 5 minutes.
- Draw the product into a sterile syringe using the filter needle provided.
- Remove the needle from the syringe.

Usually the solution is clear. Do not use solutions that are cloudy or have deposits.

Administration:

Once reconstituted, the solution must be administered immediately, intravenously, as a single dose. Connect the syringe to an intravenous or epicranial needle; expel the air from the syringe, disinfect the skin and inject into the vein.

Inject slowly, intravenously, as a single dose immediately after reconstitution, without exceeding a flow rate of 4 ml/minute.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

March 2009