The European Agency for the Evaluation of Medicinal Products
*Evaluation of Medicines for Human Use*

London, 29 June 2000
CPMP/BPWG/1625/99

# COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

# CORE SPC FOR HUMAN PLASMA DERIVED AND RECOMBINANT COAGULATION FACTOR IX PRODUCTS

| | |
|---|---|
| **DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP** | June 1999 |
| **TRANSMISSION TO THE CPMP** | June 1999 |
| **RELEASE FOR CONSULTATION** | June 1999 |
| **DEADLINE FOR COMMENTS** | December 1999 |
| **DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY** | April 2000 |
| **DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP** | May 2000 |
| **TRANSMISSION TO THE CPMP** | May 2000 |
| **FINAL ADOPTION BY THE CPMP** | June 2000 |
| **DATE FOR COMING INTO OPERATION** | December 2000 |

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-20) 74 18 84 00 Fax (+44-20) 74 18 85 45
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

**CORE SPC**
**FOR**
**HUMAN PLASMA DERIVED AND RECOMBINANT COAGULATION FACTOR IX PRODUCTS**

*The EMEA template for Summary of Product Characteristics and the QRD convention provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*

QRD convention to be followed for EMEA templates
Product information template with explanatory notes

The following convention is used in this core SPC:
- <dot underlined text> for plasma derived
- <wave-underlined text> for recombinant

## 1. NAME OF THE MEDICINAL PRODUCT

{(Trade) name of product <strength> <pharmaceutical form>}

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*[Product specific information on quantitative composition as nominal potency per container and nominal potency per ml <after reconstitution> and nominal potency per x ml <after reconstitution>. Volume of solvent for reconstitution. Method of potency determination. Specific activity.*

*For recombinant products, comparison of structure with the plasma derived coagulation factor. The suggested general statement on the structure and cell line should be adapted to reflect the product specific characteristics.]*

{(Trade) name of product} is presented as a {pharmaceutical form} containing nominally {x} *[as per labelled content]* IU <human ><{INN}, recombinant> coagulation factor IX per {container}.

The product contains approximately {x} IU/ml ({y}IU/{z}ml) <human ><{INN}, recombinant> coagulation factor IX <when reconstituted with {z} ml of *[define solvent]*>.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting test. The specific activity of {(Trade) name of product} is approximately {x} IU/mg protein.

<{(Trade) name of the product} contains recombinant coagulation factor IX (INN={insert}). {INN} (recombinant coagulation factor IX) is a purified protein that has {x} amino acids. It has an amino acid sequence that is comparable to factor IX, and post-translational modifications that are similar to those of the plasma-derived molecule. Recombinant coagulation factor IX is a glycoprotein that is secreted by genetically engineered {type of cells e.g. mammalian} cells derived from a {define cell line} cell line.>

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

*[Product specific]*

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).
<This product may be used in the management of acquired 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 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by [x]% of normal activity. The required dosage is determined using the following formula:

**Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x {reciprocal of observed recovery}**

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

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in <% of normal> <IU/dl>) 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 bleeding or oral bleeding | 20-40 | Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved. |
| More extensive haemarthrosis, muscle bleeding or haematoma | 30-60 | Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved. |
| Life-threatening haemorrhages | 60-100 | Repeat infusion every 8 to 24 hours until threat is resolved |
| **Surgery** | | |
| *Minor* including tooth extraction | 30-60 | Every 24 hours, at least 1 day, until healing is achieved. |
| *Major* | 80-100 (pre- and postoperative) | 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% to 60% (IU/dl) |

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 kilogram of body weight at intervals of 3 to 4 days.>
<For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are {x} to {y} IU of factor IX per kg of body weight at intervals of {x} to {y} days.>
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

*[Where indicated in children, provide information on whether dose and frequency of administration differs. Where there are insufficient data to recommend use in children include the following:*<There are insufficient data to recommend the use of {(trade) name of the product} in children less than 6 years of age>*]*

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, FVIX 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 4.4.

**Method of administration**

<Dissolve the preparation as described at 6.6.> The product should be administered via the intravenous route. *[A recommendation for maximal rate of infusion should be given.]*

## 4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients
*[Product specific]*
<Known allergic reaction to mouse protein.>
<Known allergic reaction to <bovine> <mouse> <and/or> <hamster> protein.>

## 4.4 Special warnings and special precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. *[Product specific]* <The product contains traces of <mouse> <bovine> <hamster> <proteins> <and> <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.

*[The choice of text indicated between <> depends on whether inactivation/removal procedures in the production process are effective for the specified virus.]*
<When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV
- testing of plasma pools for HCV genomic material
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV<, HAV> <, parvovirus B19> and HBV.

<The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as <HAV > <and/or> parvovirus B19.>

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

<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).>

After repeated treatment with <human> <recombinant> 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 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 {Trade name of product} should be weighed against the risk of these complications.

In the interest of patients, it is recommended that, whenever possible, every time that{name of the product} is administered to them, the name and batch number of the product is registered.

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

<No interactions of <human> <recombinant> 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 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

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 infrequently in patients treated with 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).

Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

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. *[The experience in previously*

*untreated patients should be indicated, including the cumulative incidence of inhibitors and maximum titer of inhibitor. For example*: <In ongoing trials {x} out of {y} ({z}%) previously untreated patients treated with {(trade) name of the product} developed inhibitors: {x} out of {y} {(z%)} with a titre above 10 BU and {x} out of {y} ({z}%) with a titre below 10 BU. The median number of exposure days in these patients were {x} days (range{y-z}days).>*] [Any inhibitor development in previously treated patients should be indicated.]*

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.

<Very rarely development of antibodies to <mouse> <bovine> <and/or> <hamster> protein with related hypersensitivity reactions has been observed.>

For information on viral safety see 4.4.

### 4.9 Overdose

<No symptoms of overdose with <human> <recombinant> 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 results 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.

*Data on children less than 6 years of age treated with the product should be described.*

### 5.2 Pharmacokinetic properties

*[Product specific]*
*[Description of:*
- *incremental recovery*
- *area under the curve (AUC)*
- *half-life (both the initial phase and elimination half-life)*
- *mean residence time (MRT)*
- *clearance]*

### 5.3 Preclinical safety data

*[Product specific]*

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*[Product specific]*

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.
<Only the provided <injection> <infusion> sets should be used because treatment failure can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some <injection> <infusion> equipment.> *[If an injection/infusion set is not provided, information should be included on suitable injection /infusion sets]*.

### 6.3 Shelf life

*[Product specific]*

### 6.4 Special precautions for storage

*[Product specific]*

### 6.5 Nature and contents of container

*[Product specific]*

### 6.6 Instructions for use and handling, and disposal

*[Product specific]*

*[Product specific:* {Instructions for reconstitution}*]*
Any unused product or waste material should be disposed of in accordance with local requirements.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. <Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

## 7. MARKETING AUTHORISATION HOLDER

*[Product specific]*

## 8. MARKETING AUTHORISATION NUMBER(S)

*[Product specific]*

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

*[Product specific]*

## 10. DATE OF REVISION OF THE TEXT

*[Product specific]*