European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 19 July 2007
Doc. Ref. EMEA/CPMP/BPWG/1625/1999 – Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON CORE SPC FOR HUMAN PLASMA DERIVED AND RECOMBINANT COAGULATION FACTOR IX PRODUCTS – Rev. 1

DRAFT AGREED BY BLOOD PRODUCTS WORKING GROUP	June 1999
ADOPTION BY CPMP FOR RELEASE FOR CONSULTATION	June 1999
DEADLINE FOR COMMENTS	December 1999
DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY	April 2000
AGREED BY BLOOD PRODUCTS WORKING GROUP	May 2000
ADOPTION BY THE CPMP	June 2000
DATE FOR COMING INTO EFFECT	December 2000
REVISED DRAFT AGREED BY THE BLOOD PRODUCTS WORKING PARTY	June 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 July 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2008
AGREED BY BLOOD PRODUCTS WORKING PARTY	
ADOPTION BY THE CHMP	
DATE FOR COMING INTO EFFECT	

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.europa.eu http://www.emea.europa.eu

Comments should be provided using this template to Ludmila.svobodova@emea.europa.eu Fax +44 20 7418 8545

KEYWORDS	Human plasma derived and recombinant coagulation factor IX products, haemophilia B

EXECUTIVE SUMMARY

This guideline describes the information to be included in the Summary of Product Characteristics (SPC) for human plasma derived and recombinant coagulation factor IX products, which are indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

1. INTRODUCTION (background)

The purpose of this core SPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SPC) for human plasma derived and recombinant coagulation factor IX products, which are indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

The QRD Product Information template with explanatory notes* and the convention to be followed for QRD templates** 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.

In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the "Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products" (CPMP/BPWG/BWP/561/03).***

The following convention is used in this core SPC:

-<dot underlined text> for plasma derived

-<wave-underlined text> for rDNA

2. SCOPE

This core SPC covers human plasma derived and recombinant coagulation factor IX products. The human coagulation factor IX is defined by the European Pharmacopoeia Monograph (1223).

3. LEGAL BASIS

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended

4. MAIN GUIDELINE TEXT

* *http://www.emea.eu.int/htms/human/qrd/qrdplt/AnnotatedTemplate-H.pdf*

** *http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconvention.pdf*

*** *http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf*

1. NAME OF THE MEDICINAL PRODUCT

[Product specific]

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: concise description/characterisation of protein structure in comparison to the plasma derived coagulation factor. The suggested general statement on the structure and cell line should be adapted to reflect the product specific characteristics.]

Each {container} contains nominally {x} *[as per labelled content]* IU human coagulation factor IX <(rDNA),{INN}>.

One ml of {(Invented) name} contains approximately {x} IU ({y}IU/{z}ml) of human coagulation factor IX <(rDNA), {INN}><after reconstitution>.

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

<{INN} (recombinant coagulation factor IX) is a purified protein that has {x} amino acids. It has an amino acid sequence that is comparable to plasma-derived factor IX, and post-translational modifications that are similar to those of the plasma-derived molecule. Recombinant coagulation factor IX is produced by recombinant DNA technology in {cell line}.>

[Product specific information on excipients]

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.

On demand treatment

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 surgery* including tooth extraction	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	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)

Prophylaxis

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

<*Continuous infusion*

Prior to surgery, a pharmacokinetic analysis should be performed to obtain an estimate of clearance. The initial infusion rate can be calculated as follows: Clearance x desired steady state level = infusion rate (IU/kg/hr).
After the initial 24 hours of continuous infusion, the clearance should be calculated again every day using the steady state equation with the measured level and the known rate of infusion.>

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.

[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 {(invented) name of the product} in children less than 6 years of age><There is no experience in children> <(see section <4.4> <5.2>)>.> <The experience in children is limited. (see section 5.1)>

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 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, standard medical treatment for shock should be implemented.

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03]

After repeated treatment with human coagulation factor IX <(rDNA)> 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 products, 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 products 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 {(Invented) name of product} 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 <(rDNA)> products with other medicinal products have been reported.>

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

{Invented name} has no influence on the ability to drive and use machines

4.8 Undesirable effects

The following adverse reactions have been reported <from {x} patients in clinical studies> <and from post-marketing experience>:

[This section should be prepared in line with the general provisions of the SPC guideline.]

MedDRA Standard System Organ Class	Adverse reactions	Frequency

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 titre of inhibitor. For example*: <In ongoing trials {x} out of {y} ({z}%) previously untreated patients treated with {(invented) name of the product} developed inhibitors: {x} out of {y} {(z%)} with a titre above 5 BU and {x} out of {y} ({z}%) with a titre below 5 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.>

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03]

4.9 Overdose

<No case of overdose has 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 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)*
- *clearance]*

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

In the absence of compatibility studies, 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 Special precautions for disposal <and other handling>

[Product specific]

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 TEXT

[Product specific]