EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2018
EMA/CHMP/BPWP/1625/1999 rev. 3
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products

Draft

Revised draft agreed by the Blood Products Working Party	August 2018
Adopted by Committee for Medicinal Products for Human Use (CHMP)	15 November 2018
Start of public consultation	3 December 2018
End of public consultation	30 June 2019

This guideline replaces 'Guideline on core SmPC with reference number (EMA/CHMP/BPWP/1625/1999 rev.2)'.

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products

Table of contents

Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) 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 SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SmPC) 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). Guidance on the conduct of clinical trials for factor IX products is given in the "Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products" (EMA/CHMP/BPWP/144552/2009) which should be considered in connection with the core SmPC.

This core SmPC addresses specific aspects related to factor IX products, for general wording and structural aspects, the SmPC guideline and QRD template should be followed. The QRD product information template with explanatory notes ('QRD annotated template')[1] and the convention to be followed for QRD templates[2] provide general guidance on format and text and should be read in conjunction with the core SmPC and the Guideline on summary of product characteristics[3].

In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the "Guideline on the Warning on Transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products" (CHMP/BWP/360642/2010 rev. 1).[4]

Timeline history of core SmPC: The original core SmPC (EMA/CHMP/BPWP/1625/1999) came into operation in December 2000. Revision 1 came into effect in December 2012. Revision 2 was a rapid revision following the 2013 EMA/EDQM workshop on potency assays to highlight that there can be significantly discrepant assay results in clinical monitoring depending on the assay used.

In July 2015 an EMA workshop exploring on registries in haemophilia came to the recommendation that the clinical trial concept requiring PUP studies for FIX products needs to be reconsidered. In light of increasing scientific knowledge the number of suitable patients especially previously untreated patients (PUPs) to be enrolled in clinical trials is problematic. Hence, the conduct of sufficiently informative clinical trials in PUPs to estimate important characteristics of single products is considered difficult. Following a public consultation in 2017, a second workshop on haemophilia registries was held on 8 June 2018 which aimed at defining the requirements for practical implementation using existing registries to support post-authorisation observational studies of haemophilia medicines. The workshop discussed recommendations on important aspects such as appropriate governance of registries, patient consent, data collection, data quality and data sharing, and interoperability between different registries. Therefore the obligation to perform clinical trials in PUPs for marketing authorisation purposes has been deleted and the core SmPC has been revised accordingly.

The opportunity is taken to make other minor updates.

[1] http://www.ema.europa.eu/htms/human/qrd/docs/Hannotatedtemplate.pdf
[2] http://www.ema.europa.eu/htms/human/qrd/docs/convention.pdf
[3] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.pdf

The following convention is used in this core SmPC:

-<dot underlined text> for plasma derived

-<wave-underlined text> for rDNA

2. Scope

This core SmPC covers human plasma derived and recombinant coagulation factor IX products including new developments of factor IX (e.g. long-acting products). The SmPC for a long-acting product should be adapted from the core SmPC, particularly in 4.2 posology, to reflect the characteristics of the specific product. 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.

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

{(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 protein that has {x} amino acids [*include any product specific modification*]. It is produced by recombinant DNA technology in {cell line}.>

<Produced from the plasma of human donors.>

[Product specific]

<Excipient(s) with known effect >

For the full list of *excipients* see section 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). [*Product specific: specify age range in accordance with the SmPC guideline, for example:*]

<{(Invented) name} can be used for all age groups>

<Management of acquired factor IX deficiency. [*Product specific specify age range in accordance with the SmPC guideline*.]>

4.2 Posology and method of administration

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

Treatment monitoring

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. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require

adjustment in underweight or overweight patients. 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.

[Where there can be discrepant assay results depending on the assay used for clinical monitoring, the general statement for rFIX products given below should be included and can be supplemented with product-specific information.]

When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology

Dose 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.

[Product specific:]

On demand treatment

The calculation of the required dose 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 dose 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.

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 post-operative)	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

[Product specific]

<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.

[Product specific]
<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.>

Paediatric population
[If the product is indicated in the paediatric population, posology recommendations should be given for each of the relevant subsets. If the posology is the same in adults and children, then a statement to this

effect is sufficient. If there is no indication in some or all subsets, the following statement(s) should be used.]

<The safety and efficacy of {(invented) name} in children aged x to y <months, years> have not yet been established.
<No data are available.> <Currently available data are described in section <4.8><5.1><5.2> but no recommendation on a posology can be made.>

Method of administration
Intravenous use.

[A recommendation for maximal rate of infusion should be given.]

<For instructions on dilution of the medicinal product before administration, see section 6.>

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

[*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

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions are possible with {(invented) name}. *[Product specific]* <The product contains traces of <mouse> <bovine> <hamster> <proteins> <and> <human proteins other than factor IX>.>. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
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.

Thromboembolism
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.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

[The following to be included for all products where a central venous access device (CVAD) will be required.]

<Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.>

[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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).]

[The following text from the guideline on the Warning on transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010) should also be included for recombinant products.]

Paediatric population

[Product specific]

<The listed warnings and precautions apply both to adults and children.>

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.>

Paediatric population

[Product specific]

<The listed interactions apply both to adults and children.>

4.6 Fertility, 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.

[Any relevant product specific information should be added.]

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

Summary of the safety profile

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 rarely and may in some cases progress to severe anaphylaxis (including shock). 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.

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

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 adverse reactions.

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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

<Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.>

MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency**{<Very common, common, uncommon, rare, very rare.>}

Description of selected adverse reactions

[Product specific]

Paediatric population

[Product specific]

<Frequency, type and severity of adverse reactions in children are <expected to be> the same as in adults.>

<Other special population(s)>

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

[Any known information should be added.]

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.

Of note, ABR (annualized bleeding rate) is not comparable between different factor concentrates and between different clinical studies.

Paediatric population

[Product specific: The text should be in line with the Paediatric Regulation and the SmPC guideline. In case of a full waiver or any deferral, include the standard statement in the SmPC guideline.]

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]*

Paediatric population

[Product specific]

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: reference should be made to the SmPC guideline for stability at different temporary storage conditions.]

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]

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

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

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]

<Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. >