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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

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

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KEYWORDS	Human plasma derived and recombinant coagulation factor VIII products, haemophilia A

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 VIII products, which are indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII 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 VIII products, which is indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII 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 VIII products. The human coagulation factor VIII is defined by the Ph. Eur. Monograph (0275) and the human coagulation factor VIII (rDNA) by the Ph. Eur. Monograph (1643).

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 VIII <(rDNA), {INN}>.

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

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

<{INN} (human coagulation factor VIII (rDNA)) is a purified protein that has {x} amino acids. It has an amino acid sequence that is comparable to plasma-derived factor VIII, and post-translational modifications that are similar to those of the plasma-derived molecule. Human coagulation factor VIII (rDNA) 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 A (congenital factor VIII deficiency).

<This product may be used in the management of acquired factor VIII deficiency.>

[Product specific]

<This preparation does not contain von Willebrand factor <in pharmacologically effective quantities> and is therefore not indicated in von Willebrand's disease.>

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 VIII 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 VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII 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 VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by <x% to y% of normal activity> <x-y IU/dl>. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor VIII 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 VIII 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 VIII level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12 to 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 12-24 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 VIII activity of 30% to 60% (IU/dl)

Prophylaxis

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 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.>

During the course of treatment, appropriate determination of factor VIII 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 VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, 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 VIII inhibitors. If the expected factor VIII 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 VIII inhibitor is present. In patients with high levels of inhibitor, factor VIII 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 VIII>.> 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]

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one FVIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory test.

See also 4.8. Undesirable effects.

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

<No interactions of human coagulation factor VIII ≤(rDNA)> products with other medicinal products have been reported.>

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII 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, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. 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.]*

<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 VIII, ATC code: B02BD02.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

[Product specific]

<In addition to its role as a factor VIII protecting protein, von Willebrand mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.>

[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 VIII 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]