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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

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

Draft

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This guideline (EMA/CHMP/BPWP/1619/1999 rev. 2) replaces guideline on core SPC with reference number CPMP/BPWG/1619/1999 rev. 1.

Changes from the previous guideline are indicated by underlined text and strike through; the public consultation is restricted to these changes.

Comments should be provided using this template. The completed comments form should be sent to BPWPsecretariat@ema.europa.eu

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

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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 VIII products, which are indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

In case of an indication claim in von Willebrand's disease, see also core SmPC for von Willebrand factor products (CPMP/BPWG/278/02).

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 VIII products, which are indicated for use in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Guidance on the conduct of clinical trials for factor VIII products is given in the "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009) which should be considered in connection with the core SmPC.

This core SmPC addresses specific aspects related to factor VIII 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 "Note for Guidance on the Warning on Transmissible Agents in SmPCs and Package Leaflets for plasma-derived medicinal products" (EMA/CHMP/BWP/360642/2010 rev. 1).[4]

Timeline history of core SmPC: The original core SPC (CPMP/BPWG/1619/99) came into operation in December 2000. Revision 1 came into effect in December 2012. Revision 2 is 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. The opportunity is taken to make other minor updates.

The following convention is used in this core SmPC:

- <dot underlined text> for plasma derived
- <wave-underlined text> for rDNA

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005091.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

2. Scope

This core SmPC covers human plasma derived and recombinant coagulation factor VIII products including new developments of factor VIII (e.g. long-acting products). The SmPC for new factor VIII products (e.g. long-acting products) should be adapted from the core SmPC where applicable, particularly in 4.2. Posology and method of administration, to reflect the characteristics of the specific product. Human coagulation factor VIII is defined by the Ph. Eur. Monograph (0275) and human coagulation factor VIII (rDNA) by the Ph. Eur. Monograph (1643).

For Immune Tolerance Induction (ITI) a separate reflection paper is ~~under development~~ available.

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 VIII <(rDNA), {INN}>.

{(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 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*]

<This preparation contains human von Willebrand factor.>

<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 A (congenital factor VIII 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 VIII 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.

[Product specific for products where a study in PUPs is required but results are not yet available – see clinical guideline for further details:]

<Previously untreated patients
The safety and efficacy of {(Invented) name} in previously untreated patients have not yet been established. No data are available. >

Treatment monitoring
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. Individual patients may vary in their response to factor VIII, 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 VIII activity) is indispensable.

[*Where there can be discrepant assay results depending on the assay used for clinical monitoring, the statement 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 VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay.>

Posology
The dose 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.

~~*[Product Specific]*~~
The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably 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.

[Product specific:]

On demand treatment
The calculation of the required dose 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 dose 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 post-operative)	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

[Product specific]

<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, demonstrating different half-lives and recoveries.~~

~~*<Previously untreated patients*~~

~~[Product specific – see clinical guideline for further details] The safety and efficacy of {(invented) name} in previously untreated patients 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.>~~

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 precautions for use

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 VIII>.> 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

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 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 factor VIII 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 all 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 tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. 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 haemophilia and factor VIII inhibitors.

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

[The following to be included for all medicinal 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.]

It is strongly recommended that every time that {(invented) name} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

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 VIII <(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 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.

[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).

<Very rarely development of antibodies to <mouse> <bovine> <and/or> <hamster> protein with related hypersensitivity reactions 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 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 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 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 factor mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.>

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 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: 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.>