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Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

CORE SPC FOR HUMAN PLASMA DERIVED AND RECOMBINANT COAGULATION FACTOR VIII PRODUCTS

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CORE SPC
FOR
HUMAN PLASMA DERIVED AND RECOMBINANT COAGULATION FACTOR VIII 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 VIII per {container}.

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

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

<{(Trade) name of the product} contains recombinant coagulation factor VIII (INN={insert}). {INN} (recombinant coagulation factor VIII) is a purified protein that has {x} amino acids. It has an amino acid sequence that is comparable to factor VIII, and post-translational modifications that are similar to those of the plasma-derived molecule. Recombinant coagulation factor VIII 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 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.

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 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 VIII activity of 30% to 60% (IU/dl)

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.

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.

[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 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, 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 the 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 VIII 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).>

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. Patients treated with <human> <recombinant> coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory test. See also 4.8. Undesirable effects.

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 VIII products with other medicinal products are known.>

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

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, 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 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.]*

<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 VIII have 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 a 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)*
- *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 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 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 TEXT

[Product specific]