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Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CORE SPC FOR HUMAN PLASMA DERIVED von WILLEBRAND FACTOR (CPMP/BPWG/278/02)

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Note:
This Core SPC is intended to cover the indication for von Willebrand Disease only. The SPC for products with indications for both the treatment of Haemophilia A and von Willebrand Disease, should be a compilation of the relevant parts of the core SPC for Human Plasma Derived and Recombinant FVIII Products (CPMP/BPWG/198/95 rev.1) and of the core SPC for Human Plasma-Derived von Willebrand factor (CPMP/BPWG/278/02).

* This second consultation was specifically on Section 4.2 of the core SPC because of a complete revision of the recommendations for von Willebrand factor products with a low factor VIII content.

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CORE SPC
FOR
HUMAN PLASMA-DERIVED von WILLEBRAND FACTOR

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).****

* *(http://www.emea.eu.int/htms/human/qrd/qrdplt/01aspc52exp.pdf)*
** *(http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv6.pdf)*
*** *(http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf)*

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name 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 according to assays authorised by the Ph. Eur. Specific activity.]

{(Invented) name of product} is presented as a {pharmaceutical form} containing nominally {x}IU human von Willebrand factor (VWF) per {container}.

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

The specific activity of {(Invented) name of product} is approximately {x} IU of VWF:RCo/mg protein.

The VWF potency (IU) is measured according to ristocetin cofactor activity (VWF:RCo) <and {specify other methods e.g. collagen binding activity}> compared to the International Standard for von Willebrand factor concentrate (WHO).

The product contains approximately {x} IU/ml ({y}IU/{z}ml) human coagulation factor VIII.

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

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contra-indicated.

[Product specific]

<{(Invented) name of product} should not be used in the treatment of Haemophilia A.>

4.2 Posology and method of administration

Treatment of von Willebrand disease should be supervised by a physician experienced in the treatment of haemostatic disorders.

Posology

[Product specific]

Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 0.02 IU/ml (2 %).

Levels of VWF:RCo of > 0.6 IU/ml (60%) and of FVIII:C of > 0.4 IU/ml (40%) should be achieved.

[Product specific for von Willebrand factor product[1] containing FVIII:]

<Usually 40-80 IU/kg of von Willebrand factor (VWF:RCo) and 20-40 IU/kg of FVIII:C are recommended to achieve haemostasis.

[1] FVIII-containing von Willebrand factor products, usually contain more than 50IU of FVIII:C per 100IU of vWF:RCo.

An initial dose of 80 IU/kg of von Willebrand factor may be required, especially in patients with type 3 von Willebrand disease where maintenance of adequate levels may require greater doses than in other types of von Willebrand disease.

An appropriate dose should be re-administered every 12-24 hours. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and both vWF:RCo and FVIII:C levels.

When using a FVIII-containing von Willebrand factor product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. After 24-48 hours of treatment, in order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval or the use of a VWF product containing a low level of FVIII should be considered.>

[Product specific for von Willebrand factor product with a low FVIII content:]

<Haemostasis cannot be ensured until factor VIII coagulant activity (FVIII:C) has reached 0.4 IU/ml (40 %). Injection of von Willebrand factor alone does not induce a maximum rise of FVIII:C for at least 6-12 hours. It cannot immediately correct the FVIII:C level. So, if the patient's baseline plasma FVIII:C level is below this critical level, in all situations where a rapid correction of haemostasis should be achieved, such as treatment of haemorrhage, severe trauma or emergency surgery, it is necessary to administer a factor VIII product with the first injection of von Willebrand factor, in order to achieve a haemostatic plasma level of FVIII:C.

However, if an immediate rise in FVIII:C is not necessary, for example if the baseline FVIII:C level is sufficient to ensure haemostasis, the physician may decide to omit the co-administration of FVIII at the first injection of VWF.

- Start of treatment :
The first dose of {(Invented) name of product} is 40 to 80 IU/kg for the treatment of haemorrhage or trauma, in conjunction with the required amount of factor VIII product, calculated according to the patient's baseline plasma level of FVIII:C, in order to achieve an appropriate plasma level of FVIII:C, immediately before the intervention or as soon as possible after the onset of the bleeding episode or severe trauma. In case of surgery, it should be given 1 hour before the procedure.

An initial dose of 80 IU/kg of {(Invented) name of product} may be required, especially in patients with type 3 VWD where maintenance of adequate levels may require higher doses than in other types of VWD.

For elective surgery, treatment with {(Invented) name of product} should start 12-24 hours before surgery and should be repeated 1 hour before the procedure. In this case, co-administration of factor VIII product is not required, since endogenous FVIII:C has usually reached the critical level of 0.4 IU/ml (40 %) before surgery. However, this should be confirmed in each patient.

- Subsequent injections:
If required, treatment should be continued with an appropriate dose of {(Invented) name of product}, 40-80 kg/per day in 1 or 2 injections daily over one to several days. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and both VWF:RCo and FVIII:C levels.>

[Where indicated in children, provide information on whether dose and frequency of administration differs.]

[Where data on the use of the product in children is limited, include the following:]

<There is no data from a clinical study to characterise the response to use of the {(Invented) name of product} in children less than 6 years of age.>

Method of administration

Dissolve the preparation as described under 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 any of the constituents.

[Product specific]

4.4 Special warnings and precautions for use

<In actively bleeding patients it is recommended to co-administer a FVIII product with the von Willebrand factor product with a low FVIII content as a first line treatment.>

As with any intravenous infusion of a plasma-derived protein, allergic type hypersensitivity reactions are possible. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. 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, the administration should be discontinued immediately. 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).]

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations. *[Product specific]* <When using a factor VIII-containing von Willebrand factor product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving factor VIII-containing von Willebrand factor products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events.>

Patients with von Willebrand disease, especially type 3 patients, may develop neutralising antibodies (inhibitors) to von Willebrand factor. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a von Willebrand factor inhibitor is present. In patients with high levels of inhibitor, von Willebrand factor therapy may not be effective and other therapeutic options should be considered.

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

<No interactions of human von Willebrand factor products with other medicinal products are known.>

4.6 Pregnancy and lactation

<Animal reproduction studies have not been conducted with {(Invented) name of product}.>

[A short paragraph describing the experience of von Willebrand factor treatment in pregnant or lactating women should be added.]

{(Invented) name of product} should be administered to pregnant and lactating von Willebrand factor deficient women 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 angiodema, 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 von Willebrand disease, especially type 3 patients, may very rarely develop neutralising antibodies (inhibitors) to von Willebrand factor. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies may occur in close association with anaphylactic reactions. Therefore, patients experiencing anaphylactic reaction should be evaluated for the presence of an inhibitor.

In all such cases, it is recommended that a specialised haemophilia centre be contacted.

<Very rarely development of antibodies to <mouse> protein with related hypersensitivity reactions has been observed.>

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors.

[Product specific] <In patients receiving factor VIII-containing von Willebrand factor products sustained excessive FVIII:C plasma levels may increase the risk of thrombotic events.>

[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 symptoms of overdose with von Willebrand factor have been reported. Thromboembolic events may occur in case of major overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antihaemorrhagics: blood coagulation factors <von Willebrand factor and coagulation factor VIII in combination. ATC code: B02BD06>

{(Invented) name of the product} behaves in the same way as endogenous von Willebrand factor.

Administration of von Willebrand factor allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand's disease) at two levels:

- Von Willebrand factor re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of polymerisation of the protein.
- Von Willebrand factor produces delayed correction of the associated factor VIII deficiency. Administered intravenously, von Willebrand factor binds to endogenous factor VIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation. Because of this, administration of pure von Willebrand factor (vWF product with a low FVIII level) restores the FVIII:C level to normal as a secondary effect after the first infusion**.** Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

5.2 Pharmacokinetic properties

[Product specific]

[Description of:

- *incremental change in von Willebrand factor and factor VIII in von Willebrand factor deficient patients without clinical symptoms of bleeding (for example, 1.8% per IU/kg; injection of 50 IU/kg raises the von Willebrand factor level by about 90%).*
- *area under the curve for von Willebrand factor and factor VIII (AUC)*
- *half-life (both the initial phase and elimination half life) for von Willebrand factor and factor VIII*
- *clearance for von Willebrand factor and factor VIII]*

Peak plasma levels of von Willebrand factor usually occur within {x} minutes after injection.

[Product specific]

<Normalisation of FVIII level is progressive, varies and usually requires between 6 and 12 hours. This effect is sustained for 2 to 3 days.>

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

[Product specific]

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 von Willebrand factor 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:

- *shelf life of the medicinal product as packaged for sale*
- *shelf life after dilution or reconstitution according to directions]*

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 reconstituted 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.

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]