



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**CORE SPC FOR HUMAN PLASMA DERIVED COAGULATION
FACTOR VII PRODUCTS
(CPMP/BPWG/2048/01)**

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**CORE SPC
FOR
HUMAN PLASMA DERIVED COAGULATION FACTOR VII PRODUCTS**

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 “Guideline 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/H01a%20EN%20NOTE%20SPC-II-lab-pl%20v6.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 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.]

{(Invented) name of product} is presented as a {pharmaceutical form} containing nominally {x} [as per labelled content] IU human coagulation factor VII per {container}.

The product contains approximately {x} IU/ml ({y}IU/{z}ml) human coagulation factor VII [*The exact volume for reconstitution of the powder has to be indicated.*] <when reconstituted with {z} ml of [define solvent]> .

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

The reconstituted product contains less than { α }, { β } and { γ } IU/ml of coagulation factors II, IX and X, respectively.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of bleeding disorders caused by isolated congenital factor VII deficiency.
- Prophylaxis of bleeding disorders caused by isolated congenital factor VII deficiency associated with a history of bleeding and a residual level of factor VII:C lower than 25% of normal (0.25 IU/ml).

This preparation does not contain activated factor VIIa and should not be used in haemophiliac patients with inhibitor.

4.2 Posology and method of administration

Posology

Because of the rarity of the disease, only limited data are available on the clinical use of factor VII products. For this reason only general dosage guidelines can be given whereas individual dosage requirements can only be identified on the basis of regular determinations of factor VII plasma levels and continuous monitoring of the clinical condition of the patient.

The dosage and duration of the substitution therapy depend on the severity of the factor VII deficiency, on the location and extent of bleeding and on the patient's clinical condition. The relationship between the individual residual level of factor VII and clinical bleeding tendency is less firm than in classical haemophilia.

The number of units of factor VII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VII products. Factor VII activity in plasma is expressed either as a percentage (relative to normal plasma) or in International Units (relative to an international standard for factor VII in plasma).

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

$$\text{Required units} = \text{body weight (kg)} \times \text{desired factor VII rise IU/ml} \times \left\{ \frac{1}{\text{reciprocal of observed recovery (ml/kg)}} \right\}$$

If the individual recovery is known that value should be used for calculation.

The amount to be administered and the frequency of administration should always be oriented towards clinical efficacy in the individual case. This is especially important in treatment of factor VII deficiency, as the individual bleeding tendency is not strictly related to the factor VII activity in plasma as measured in laboratory tests. Dosage intervals must be adapted to the short circulating half-life of factor VII of approximately 3 to 5 hours. When {(invented) name of product} is administered by intermittent injections/infusions, dosage intervals of 6-8 hours are often adequate. Usually in the treatment of factor VII deficiency, lower levels of the deficient factor, in relation to the activity in normal plasma, are required as compared to classical haemophilia (haemophilia A and B). The table below gives some guidance for administration by intermittent injections/infusions based on the limited clinical experience. Medical evidence based on clinical efficacy trials does not exist.

Degree of haemorrhage/ Type of surgical procedure	Factor VII level required IU/ml	Frequency of doses (hours)/ Duration of therapy (days)
Minor haemorrhage	0.10-0.20	A single dose
Severe bleeding	0.25-0.40 (trough-peak)	For 8 – 10 days or until complete healing*
Minor surgical interventions	0.20-0.30	A single dose before surgery or, if estimated bleeding risk is more pronounced, until wound healing
Major surgical interventions	Pre-operative > 0.50 Then 0.25-0.45 (trough-peak)	For 8 to 10 days or until complete wound healing*

* Based on clinical judgement in the individual case, lower doses could be sufficient towards the end of treatment provided that adequate haemostasis is achieved.

[Product specific]{Dosage recommendation for continuous infusion}

[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 product} in children less than 6 years of age>]

Method of administration

<Dissolve the product as described at 6.6.> The product should be administered via the intravenous route. *[A recommendation for maximal rate of injection/ infusion should be given].*

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

High risk of thrombosis or disseminated intravascular coagulation (see 4.4).

<[To be added in the case of heparin as a constituent only:]

Known allergy to heparin or history of heparin induced thrombocytopenia>

4.4 Special warnings and special precautions for use

If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented. Patients should be informed of the early signs of hypersensitivity reactions. If such symptoms occur, the patient should be advised to discontinue use of the product immediately and contact their physician.

[The text to be inserted here for the warning on 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 thrombosis or disseminated intravascular coagulation when patients are treated with human coagulation factor VII containing product. Patients given human coagulation factor VII should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, caution should be exercised when administering human coagulation factor VII to patients with a history of coronary heart disease, to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with {(invented) name of product} should be weighed against the risk of these complications.

4.5 Interactions with other medicinal products and other forms of interactions

No interactions of human coagulation factor VII with other medicinal products are known.

<Laboratory test interactions

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human factor VII, the heparin administered with the product must be taken into account. >

4.6 Pregnancy and lactation

The safety of human coagulation factor VII for use in human pregnancy has not been established in controlled clinical trials.

Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

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

Immune system disorders:

Replacement therapy with human factor VII may rarely lead to the formation of circulating antibodies inhibiting factor VII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response.

Allergic or anaphylactic-type reactions are observed in rare cases.

General disorders and administration site conditions:

Increase in body temperature is observed in rare cases.

Vascular disorders:

Thromboembolic episodes following the administration of human coagulation factor VII may occur rarely (see section 4.4).

[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

4.9 Overdose

The use of high doses of factor VII containing products (prothrombin complex products) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism.

Therefore, in case of overdosage, the risk for development of thromboembolic complications is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihæmorrhagics

- Coagulation factor VII, ATC code: B02 BD 05

Factor VII is one of the vitamin K-dependent clotting factors found in normal human plasma. It is a single chain glycoprotein with a molecular mass of approximately 50,000 Dalton. Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The Tissue Factor-factor VIIa complex activates coagulation factors IX and X, whereby factor IXa and Xa are formed. With further propagation of the coagulation cascade thrombin is generated, fibrinogen is converted to fibrin and a clot is formed. The normal generation of thrombin is also of vital importance for platelet function as a part of primary hæmostasis. Inherited factor VII deficiency is an autosomal recessive disorder. The administration of human factor VII provides an increase in plasma levels of factor VII and can temporarily correct the coagulation defect of patients with factor VII deficiency.

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 including heparin.

<Only the provided <injection> <infusion> sets should be used because treatment failure can occur as a consequence of human plasma factor VII adsorption to the internal surface 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 and reconstitution time}]

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

The colour can vary from colourless to pale-yellow up to light brown. Do not use solutions that are cloudy or have deposits. <Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

<After reconstitution the product should be used immediately.>

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 THE TEXT

[Product specific]