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Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for Human Fibrinogen Products

Draft

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This guideline replaces Guideline on core SmPC for human fibrinogen products (EMEA/CHMP/BPWP/122007/2005)

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

Keywords	*Human fibrinogen, congenital and acquired hypofibrinogenaemia, congenital dys- or afibrinogenaemia*

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Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for Human Fibrinogen, which is indicated for the treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency and as a complementary therapy to management of uncontrolled severe haemorrhage in acquired hypofibrinogenaemia.

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 Fibrinogen, which is indicated for use in the treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency and as a complementary therapy to management of uncontrolled severe haemorrhage in acquired hypofibrinogenaemia.

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 Guideline 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 the core SmPC: The original core SmPC was contained in the European Commission Medicinal Products Derived from Human Blood or Plasma, Core Summaries of Product Characteristics dated Sept – Oct – Dec 1992. This was superseded by the Guideline on the core SmPC (EMEA/CHMP/BPWP/122007/2005) that came into effect on 1 August 2009. Revision 1 updates the text on acquired hypofibrinogenaemia in Section 4.4 Special warnings and precautions for use.

2. Scope

This core SmPC covers Human Fibrinogen defined by the European Pharmacopoeia monograph 0024.

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] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/12/WC500029823.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

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

[Strength expressed as content of fibrinogen in grams per container]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Fibrinogen

[Product specific information on quantitative composition as nominal potency per container and nominal potency after reconstitution (x g/ml). Volume of solvent for reconstitution. Method of potency determination (coagulometric assay or reference to European Pharmacopoeia method). Specific activity.]

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

[Product specific, including visual description of the product, e.g. white or pale yellow powder in a vial]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency.

As complementary therapy to management of uncontrolled severe haemorrhage in acquired hypofibrinogenaemia, for example:

a. Increased consumption of fibrinogen associated with otherwise uncontrolled life-threatening bleeding in obstetric complications
b. Impaired synthesis of fibrinogen in patients with severe hepatic insufficiency

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

Posology

The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition.

The (functional) fibrinogen level should be determined in order to calculate individual dosage and the amount and frequency of administration should be determined on an individual patient basis by regular measurement of plasma fibrinogen level and continuous monitoring of the clinical condition of the patient and other replacement therapies used.

Normal plasma fibrinogen level is in the range of 1.5-4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.

In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

1. Prophylaxis in patients with congenital hypo-, dys- or afibrinogenaemia and known bleeding tendency.

To prevent excessive bleeding during surgical procedures, prophylactic treatment is recommended to raise fibrinogen levels to 1 g/l and maintain fibrinogen at this level until haemostasis is secure and above 0.5 g/l until wound healing is complete.

In case of surgical procedure or treatment of a bleeding episode, the dose should be calculated as follows:

Dose (g) = (desired levels (g/l) – baseline level (g/l) x 1/recovery (g/l / g/kg) x body weight (kg).
[Product specific information on recovery in study populations should be included if available.].

Subsequent posology (doses and frequency of injections) should be adapted based on the patient's clinical status and laboratory results.

The biological half-life of fibrinogen is 3-4 days. Thus, in the absence of consumption, repeated treatment with human fibrinogen is not usually required. Given the accumulation that occurs in case of repeated administration for a prophylactic use, the dose and the frequency should be determined according to the therapeutic goals of the physician for a given patient.

2. Treatment of bleeding

Adults

Generally 1-2 g is administered initially with subsequent infusions as required. In case of severe haemorrhage i.e. obstetric use/abruption placenta, large amounts (4-8 g) of fibrinogen may be required.

Children

The dosage should be determined according to the body weight and clinical need but is usually 20-30 mg/kg.

Method of Administration

Intravenous infusion or injection

{Invented name of the product} should be administered slowly intravenously.

For instructions on reconstitution of the product before administration, see section 6.2 and 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
[Product specific for products containing heparin:]
<Known allergy to heparin or history of heparin induced thrombocytopenia type II.>

4.4 Special warnings and precautions for use

There is a risk of thrombosis when patients, with either congenital or acquired deficiency, are treated with human fibrinogen particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.

In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in peri- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human plasma fibrinogen should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

Acquired hypofibrinogenaemia is associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors should be considered (with or without administration of fibrinogen concentrate). Careful monitoring of the coagulation system is necessary.

Deleted: Taking into consideration that in cases of acquired hypofibrinogenaemia (particularly in the case of disseminated intravascular coagulation and liver disease) there is no isolated deficiency of fibrinogen, but deficiency of all coagulation factors and inhibitors is usual, the use of multifactor, balanced replacement with fresh frozen plasma, cryoprecipitate or several factor and inhibitor products has to be considered as first line therapy and careful monitoring of the coagulation system is necessary. ¶
¶

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

[Product specific for products containing heparin:]

<Interference with clotting tests>

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human fibrinogen, the heparin as a constituent of the administered product must be taken into account.>

[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 rev. 1).]

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data with fibrinogen.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human fibrinogen products with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

The safety of human plasma fibrinogen products for use in human pregnancy and during lactation has not been established in controlled clinical trials.

Clinical experience with fibrinogen products in the treatment of obstetric complications suggests that no harmful effects on the course of the pregnancy or health of the foetus or the neonate are to be expected.

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

< There are no robust data on the frequency of adverse reactions from clinical trials. The following adverse reactions have been reported.>

< The following adverse reactions have been reported <from {x} patients in clinical studies><and from post-marketing experience>>

[If there are robust data on the frequency of undesirable effects from clinical trials the section should be prepared in line with the general provisions of the SmPC guideline]

MedDRA Standard System Organ Class	**Undesirable effects**	**<Frequency>**
Immune system disorders:	Allergic or anaphylactic-type reactions	
Vascular disorders:	Thromboembolic episodes (including myocardial infarction and pulmonary embolism) (see section 4.4)	
General disorders and administration site conditions:	Increase in body temperature	

[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 rev. 1).]

4.9 Overdose

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated (see 4.2).

In case of overdosage, the risk of development of thromboembolic complications is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, human fibrinogen, ATC code: B02BB01

Human fibrinogen (coagulation factor I), in the presence of thrombin, activated coagulation factor XIII (F XIIIa) and calcium ions, is converted into a stable and elastic three-dimensional fibrin haemostatic clot.

The administration of human fibrinogen provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency.

5.2 Pharmacokinetic properties

[Product specific]

In plasma, the biological half-life of fibrinogen is 3-4 days.

The product is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.

5.3 Preclinical safety data

[Product specific]

[Thrombogenicity testing: 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 and should be administered by a separate injection/infusion line.

<Only the provided <injection> <infusion> sets should be used because treatment failure can occur as a consequence of coagulation factor 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]

The product, after reconstitution, should be used immediately and not stored.

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: {Instructions for reconstitution including reconstitution time}*]*

The solution should be almost colourless. Do not use solutions that are cloudy or have deposits.

<Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

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 THE TEXT

[Product specific]