European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CORE SPC FOR HUMAN PLASMA FIBRINOGEN PRODUCTS (EMEA/CHMP/BPWP/122007/2005)

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This Guideline replaces the core SPC contained in the European Commission Medicinal Products Derived from Human Blood or Plasma, Core Summaries of Product Characteristics dated Sept – Oct – Dec 1992.

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KEYWORDS	Human fibrinogen, congenital and acquired hypofibrinogenaemia, congenital dys- or afibrinogenaemia

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CORE SPC
FOR
HUMAN PLASMA FIBRINOGEN 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 "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/AnnotatedTemplate-H.pdf
** http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconvention.pdf
*** http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf

1. NAME OF 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.]

For a 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

1. As replacement therapy in congenital hypo-, dys- or afibrinogenaemia in patients with bleeding tendency, for perioperative prophylaxis and before or during pregnancy and obstetrics.

2. As complementary therapy to management of life threating bleeding in cases of acquired hypofibrinogenaemia e.g.:

    a) Increased consumption of fibrinogen associated with otherwise uncontrolled life-threating bleeding in obstetric complications,

    b) Dilutional hypofibrinogenemia in, for example, trauma-patients with severe blood loss after massive replacement therapy with colloid and crystalloid solutions,

    c) Disorders of synthesis of coagulation factors – e.g. severe liver parenchymal damage with fibrinogen deficiency,

    d) Increased consumption of fibrinogen associated with otherwise uncontrolled life-threating bleeding due to disseminated intravascular coagulation syndrome and hyperfibrinolysis.

4.2 Posology and method of administration

Posology
Only general dosage guidelines are given below. 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 1 g/l.

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

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

1. In congenital hypo-, dys- or afibrinogenaemia (in patients with a known bleeding tendency)

Patients with congenital hypo-, dys or afibrinogenaemia and personal or family history of bleeding and thrombosis usually require the administration of fibrinogen.
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.

2. In acquired hypofibrinogenaemia as a complementary management of bleeding

Adults
Generally 1-2 g is administered initially with subsequent infusions as required. In case of severe haemorrhage e.g. 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 e.g. 20-30 mg/kg.

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.

[If product specific information on recovery in study populations is available, the approximate figures given above should preferably be substituted by such data.]

Method of Administration
Intravenous infusion or injection

For instructions on reconstitution of the product before administration, see section 6.6.
{Invented name of the product} should be administered slowly intravenously.
[A recommendation for maximal rate of injection/ infusion should be given].

4.3 Contraindications

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

[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

The advice of a specialist experienced in the management of coagulation disorders should be sought.

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

Because of the risk of thromboembolic complications, caution and close monitoring should be performed when administering human fibrinogen concentrate to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to peri- or post-operative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with human plasma fibrinogen concentrate should be weighed against the risk of these complications.

Taking in consideration, that in case 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 replacement with fresh frozen plasma, cryoprecipitate or several factor and inhibitor concentrates has to be considered as first line therapy and careful monitoring of 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.

[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).]

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 concentrate with other medicinal products are known.

[Product specific for products containing heparin:]
<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.>

4.6 Pregnancy and lactation

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

Clinical experience with fibrinogen concentrate 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

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

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

< The following undesirable effects 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 SPC guideline]

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

[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

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated.
In case of overdosage, the risk of development of thromboembolic complications is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors I, 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 concentrate 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]

The exogenously administered human fibrinogen acts like endogenous fibrinogen, a normal constituent of the human plasma.

In animals, single dose toxicity testing is of no relevance since higher doses result in overloading. Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein. Since clinical experience provided no hint for tumourigenic or

mutagenic effects of human fibrinogen concentrate, experimental studies, particularly in heterologous species, are not considered necessary.

[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]