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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CORE SmPC FOR HUMAN PLASMA FIBRINOGEN PRODUCTS

(EMEA/CHMP/BPWP/122007/2005)

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	International Plasma Fractionation Association (IPFA)	Netherlands

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
SPECIFIC COMMENTS ON TEXT		
4.1 Therapeutic Indications		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
4.1.1	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. Comment: *This indication is too restrictive* *Preventive use for frequent or severe bleeding episodes and curative use in case of spontaneous or post-traumatic bleeding episodes are missing*.	Indication revised to clarify that it covers all relevant clinical situations: Treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency.
4.1.2	2. As complementary therapy to management of life threatening bleeding in cases of acquired hypofibrinogenaemia e.g.: Proposed change: *2. As complementary therapy to management of severe acute haemorrhage that can be associated with a decrease in plasma fibrinogen level :*	Wording of indication revised. 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
4.1.2	Comment: *Prophylaxis indication for patients treated with L Asparaginase is missing*.	Comment not accepted because it is already covered by "acquired hypofibrinogenaemia"

[1] Where applicable

4.1.2	d) Increased consumption of fibrinogen associated with otherwise uncontrolled life-threating bleeding due to disseminated intravascular coagulation syndrome and hyperfibrinolysis. Comment: *This section d) should appear just after section a) to regroup "Increased consumption".*	Comments not accepted as the order of the examples is not related to the mechanism behind the fibrinogen decrease. Furthermore, it was decided to reduce the number of examples given and this example has now been deleted.
4.2 Posology and method of administration		
4.2	**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. Comment: *Plasma fibrinogen levels should be increased to 0.5 – 1 g/l that is actually recognized as being effective in achieving normal haemostasis, cf* *Al-Mondhiry and Ehmann* *Congenital Afibrinogenemia* *American Journal of Hematology , 1994; 46: 343-347* *And* *Mannucci, Duga and Peyvandi* *Recessively inherited coagulation disorders* *Blood, 2004; 104(5): 1243-1252* *In case of severe acute haemorrhage, taking into account the volume of blood loss, the quantity rather than the concentration should be considered given the fact that fibrinogen should be polymerised to form a clot.*	Accepted

4.2	Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. Comment: *In emergency circumstances this statement is often difficult to fulfill*	The comment has been acknowledged but the recommendation is reasonable.
4.2.1	Patients with congenital hypo-, dys or afibrinogenaemia and personal or family history of bleeding and thrombosis usually require the administration of fibrinogen. Comment: *This sentence doesn't seem useful*	Comment accepted
4.2.1	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. Proposed change: *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).* *Subsequent posology (doses and frequency of injections) should be adapted based on the patient's clinical status and laboratory results.* *Given the accumulation that occurs in case of repeated treatment for a prophylactic use, the dose and the frequency should be determined according to the therapeutic goals of the physician for a given patient. This dose and frequency can be obtained by modeling further the pharmacokinetic parameters of the fibrinogen concentrate*	Comment accepted and inserted into the Core SPC apart from the last sentence. The biological half life of fibrinogen has been added.
4.2.2	2. In acquired hypofibrinogenaemia as a complementary management of bleeding Proposed change: *2. In severe acute haemorrhage as a complementary management of bleeding.*	Partially accepted, rephrased as: Treatment of bleeding

4.2.2	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.]* Comment: *Recovery of the drug should be taken into account when administering large dose of fibrinogen concentrate.*	Proposed addition is considered redundant.
4.4 Special warnings and precautions for use		
4.4	Special warnings and precautions for use Comment: *Product specific precautions should be added if excipients with known effects are present.*	This is part of the general Guideline on Summary of Product Characteristics which should be read in conjunction with the core SPC.
4.4	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. Comment: *Activated prothrombin complexes?*	Wording modified
4.4	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. Comment: *Inhibitor development?*	Comment not accepted, because antibodies can be inhibitors or non-inhibitors.

4.5 Interaction with other medicinal products and other forms of interaction		
4.5	No interactions of human fibrinogen concentrate with other medicinal products are known. Proposed change: *It should be added : However, human fibrinogen concentrate should not be mixed with other products and/or medicinal products*	See section 6.2
4.6 Pregnancy and lactation		
4.6	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. Comment: *[The safety of human plasma fibrinogen concentrate for use in human pregnancy and during lactation has not been established in controlled clinical trials.] Product specific* *However this statement is contradictory to the indication which actually includes pregnancies and obstetrics.*	Comment not accepted. The information is considered appropriately balanced.
4.8 Undesirable effects		
4.8	*[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).]* Comment: *For safety related to adventitious agents, see section 4.4.*	The proposed wording is not that given in the guideline. Cross-reference is made to the guideline for the statements to be included in SPCs in order to avoid changing all core SPCs if the wording of the guideline is changed.

5.1 Pharmacodynamic properties		
5.1	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. Proposed change: *Human fibrinogen (coagulation factor I), because human fibrinogen is used more than coagulation factor I*	Comment accepted
5.2 Pharmacokinetic properties		
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. Proposed change: *[Add a notion of observed effect duration : yield, recovery, peak, half-life] Product specific]*	The possibility to include the products specific information is already given.
5.3 Preclinical safety data		
5.3	[Product specific] Proposed change: *Add conclusions of studies which have been realized.* *[Add toxicity on reproduction and its foetal development] Product specific*	The possibility to include the products specific information is already given.