PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

Not applicable.

VI.2. ELEMENTS FOR A PUBLIC SUMMARY

Congenital fibrinogen deficiency is a hereditary disease characterised by a level less than the normal value or an absence of a protein called fibrinogen. This lack may cause coagulation disorders.

FibCLOT is used to compensate for the lack of human fibrinogen and, thus, prevent and treat bleeding (haemorrhages) in patients with congenital fibrinogen deficiency.

VI.2.1. Overview of disease epidemiology

Afibrinogenaemia is a rare disease, an inherited blood disorder in which the blood does not clot normally. It occurs when there is a complete lack (deficiency) of a protein called fibrinogen, which is needed for the blood to clot. This disease is caused by an abnormal gene that must be transmitted from both parents.

Congenital afibrinogenaemia occurs in approximately 1 in 1 million new-borns and either in males or females.

Excess bleeding is common with this condition. These episodes may be severe, or even fatal. Bleeding in the brain is the main cause of death in patients with this disorder.

To treat bleeding episodes or to prepare for surgery to treat other conditions, patients may receive: plasma (the liquid portion of the blood containing clotting factors), cryoprecipitate (a blood product containing concentrated fibrinogen and other clotting factors) or a fibrinogen concentrate through a vein (transfusion).

VI.2.2. Summary of treatment benefits

Three prospective studies have been performed in congenital deficiency: two interventional studies (41-67-113 and FGT1-A616) and one observational post-authorisation safety study (PASS-CD).

In these studies, the efficacy was evaluated by the assessment of bleeding control. Taking into account the 4-point scale, "Excellent/Good" were considered as treatment successes and "Moderate/None" as treatment failures.

- 41-67-113 was a multicenter, open-label, single arm study of FibCLOT to evaluate the safety and efficacy in patients with congenital afibrinogenaemia or hypofibrinogenemia.

  Six patients with afibrinogenaemia were included among which:
  - Four subjects were treated for a total of 21 bleeding episodes with treatment success in 20/21 bleeding episodes.
  - One subject was treated for long-term prophylaxis; no spontaneous/post-traumatic bleeding occurred.
  - One subject participated only of the clinical pharmacology part of the study.

- FGT1-A616 was a multicenter, multinational, open-label, single arm study of FibCLOT to evaluate efficacy and safety in patients with congenital afibrinogenaemia or hypofibrinogenaemia.

  Twenty patients of which 19 with afibrinogenaemia were included in the study among which sixteen in the efficacy part (each patient could be treated for different clinical situations):
  - Fifteen subjects underwent a total of 38 surgical procedures with treatment success.
  - Nine subjects were treated for a total of 32 bleeding episodes with treatment success.

- PASS was a multicenter, open-label, non-interventional, single arm post-authorisation safety study of CLOTTAFACT (human fibrinogen manufactured by LFB) in congenital and acquired deficiencies.

  Fourteen patients with afibrinogenaemia were included in the congenital deficiency part among which (each patient could be treated for different clinical situations):
  - Five patients were treated on demand with treatment success. A total of 48 bleeding episodes required a single infusion of CLOTTAFACT.
  - Nine patients were treated for long-term prophylaxis at least one year. Four patients were less than 12 years. A total of 11 spontaneous/post-traumatic bleeding episodes occurred in 5 patients and no bleeding episodes in 4 patients. No recurrent episode of intracranial hemorrhage was reported.

VI.2.3. Unknowns relating to treatment benefits

Patients with severe hepatic impairment

The exclusion of patients with severe hepatic impairment from interventional clinical trials aimed to minimise confounding factors that could influence evaluation of safety and efficacy parameters.

There was no signal, from preclinical studies, indicating that the liver could be a target organ for FibCLOT and there are no hepatic risks anticipated with human fibrinogen products.

Evaluation of clinical data did not reveal any potential hepatic risk associated with FibCLOT.

Efficacy results were not expected to be different in patients with severe hepatic impairment.

Patients with severe renal impairment

The exclusion of patients with severe renal impairment in the interventional clinical trials conducted with FibCLOT was a precautionary safety measure to minimise confounding factors that could influence the evaluation of safety parameters.

There was no signal from preclinical studies indicating that the kidney could be a target organ for FibCLOT and there are no renal risks anticipated with human fibrinogen products.

There was no case of renal impairment reported in any of clinical studies conducted with FibCLOT.

It is not anticipated that treatment with FibCLOT could have kidney implications in the target population.

Efficacy results were not expected to be different in patients with severe renal impairment.

Pregnant or breast feeding women

Pregnant or breast feeding women were not studied in any of the studies conducted with FibCLOT.

The preclinical data obtained from conventional toxicity studies have not revealed any particular risk to human beings.

There is no cause for concern about the effects of fibrinogen on fertility and general reproductive performance since fibrinogen is a normal constituent of the human body.

Efficacy results were not expected to be different in pregnant or breast feeding women.

VI.2.4. Summary of safety concerns

Important identified risks

Table 34: Important identified risks

Risk	What is known	Preventability
Allergic reactions (allergic/anaphylactic type reactions)	Allergic reactions may occur uncommonly. In some cases, these reactions have progressed to a serious allergic reaction. The warning signs of allergic reactions are swelling of the face or throat, feeling of burning and tingling at the injection site, chills, redness, itching and rash, fast heart rate, low blood pressure, extreme tiredness (lethargy), feeling sick (nausea), vomiting, restlessness, tightness of the chest, pins and needles, wheezing (asthma-like). If one of these effects occurs, alert a doctor who will, depending on the type and severity of the reaction, immediately stop this medicine and/or start an appropriate treatment. Allergic/anaphylactic like reactions have been reported for two patients in clinical studies conducted with FGTW.	Do not use FGTW if you are allergic to the active substance (human fibrinogen) or any of the other ingredients of this medicine. Inform your doctor if your are allergic to any medicine. Informing for warning signs of allergic reactions.
Blood clots (thromboembolic events {TEE})	With high dose or repeating dosing, this medicine may increase the risk of blood clots in blood vessels. Formation of blood clots may occur in the blood circulation. It may result in heart attack, stroke, a serious condition called pulmonary embolism, clot in a vein (venous thrombosis). Clots in a vein have been reported for three patients in clinical studies conducted with FGTW.	Evaluating the benefits of this medicine against the risk of blood clots: • If you have had a heart attack (history of coronary heart disease or myocardial infarction). • If you have a liver disease. • If you have just had surgery (patients postoperatively). • If you will be having surgery soon (patients preoperatively). • In new-born infants (neonates). • If you are more likely to have blood clots than normal. Performing additional tests in order to monitor this risk.

- **Important potential risks**

Table 35: Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Antibodies (also called inhibitors) (Immunogenicity)	In patients with other coagulation disorders and using other replacement therapy, antibodies (also called inhibitors) reducing the effect of the medicine could occur. No inhibitor reaction has been reported with this medicine.
Transmission of infectious agents such as viruses, emerging viruses, other not identified infective agents or pathogens (Transmission of infectious agents)	This medicine is manufactured from human plasma (the liquid part of blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include: • careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, • the testing of each donation and pools of plasma for the signs of virus infections, • the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV or AIDS virus), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (*e.g.* sickle cell disease or haemolytic anaemia). Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products. It is strongly recommended that every time you receive a dose of this medicine, the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

- **Missing information**

Table 36: Missing information

Missing information	What is known
Patients with severe hepatic impairment	There was no signal, from preclinical studies, indicating that the liver could be a target organ for FibCLOT and there are no hepatic risks anticipated with human fibrinogen products. Evaluation of clinical data did not reveal any potential hepatic risk associated with FibCLOT. However, treatment with FibCLOT in patients with severe liver disease should be assessed in terms of risk/benefit as coagulation factors synthesis could be impaired in these patients.
Patients with severe renal impairment	There was no signal from preclinical studies indicating that the kidney could be a target organ for FibCLOT and there are no renal risks anticipated with human fibrinogen products. There was no case of renal impairment reported in any of clinical studies conducted with FibCLOT. It is not anticipated that treatment with FibCLOT could have kidney implications in the target population.
Pregnant and breast feeding women	If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. This product should only be used during pregnancy and breast-feeding on the advice of your doctor. If you discover that you are pregnant during treatment, consult with you doctor as only he/she can determine whether you need to continue the treatment.

VI.2.5. Summary of risk minimisation measures by safety concern

Summary of Product Characteristics (SmPC) of FibCLOT provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

FibCLOT has no additional risk minimisation measures.

VI.2.6. Planned post-authorisation development plan

- **List of studies in post authorisation development plan**

Not applicable.

- **Studies which are a condition of the marketing authorisation**

Not applicable.

VI.2.7. Summary of changes to the Risk Management Plan over time

Not applicable.