Swiss Summary of the Risk Management Plan (RMP) for Clottafact

(Human fibrinogen)
Powder and solvent for solution for injection
1,5 g/ 100 ml

Based on EU RMP of 13 August 2015
Version number: 01

Version number CH RMP Summary: 01 (October 2016)

Opopharma Vertriebs AG
Riedmattstrasse 9
8153 Rümlang
Switzerland

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Clottafact is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

This is a summary of the risk management plan (RMP) for Clottafact which is based on the EU RMP which is an international document. Information which is Switzerland specific has been taken into account by referring to the Swissmedic approved "Arzneimittelinformation" (product information), if applicable.

10-17

This is a summary of the risk management plan (RMP) for Clottafact which is based on the EU RMP which is an international document. Information which is Switzerland specific has been taken into account by referring to the Swissmedic approved “Arzneimittelinformation” (product information), if applicable.

Overview of disease epidemiology

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.

Deficiency of fibrinogen level doesn’t concern only patient with hereditary disease, it can be an acquired disease. It occurs in major blood loss situations such as surgeries, trauma or post-partum or in patient with liver function failure or treated with L-Asparaginase.

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

Congenital fibrinogen deficiency
Congenital fibrinogen deficiency is a bleeding disorder caused by a deficiency or dysfunction of fibrinogen.

Congenital fibrinogen deficiency can be either a:
- **Quantitative deficiency** which affect partially (**hypofibrinogenaemia) or totally (afibrinogenaemia)** the quantity of fibrinogen in circulation, or a
- **Qualitative** deficiency which affect the quality (functional activity) of circulating fibrinogen **(dysfibrinogenaemia)**.

Clinical manifestations vary according to the type of deficiency. Afibrinogenaemia is a rare disease, an inherited blood disorder in which the blood does not clot normally. 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.

Acquired fibrinogen deficiency
Acquired fibrinogen deficiency can arise from a number of different clinical settings:

- in **major blood loss situations** such as surgery, trauma or postpartum hemorrhage (PPH) in which bleeding results in the consumption of coagulation factors that exceeds production. Fibrinogen level is the first factor to decrease;
    - Fibrinogen level decrease can be a consequence of **impaired fibrinogen synthesis** due to liver function failure related to chronic viral hepatitis, cirrhosis, recent transplantation or secondary to treatment with L-Asparaginase for lymphoblastic leukemia.

In view of treating bleeding episodes or in order to prepare for surgery, 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).

Summary of treatment benefits

Three prospective studies have been performed in congenital fibrinogen deficiency: two interventional studies (41-67-113, short name 113 and FGT1-A616, short name A616) and one observational post-authorisation safety study (CLOTTAFACT PASS, congenital fibrinogen deficiency part), and

Two prospective studies have been performed in acquired fibrinogen deficiency: one interventional study (FGT1-0505, short name 505) in post-partum haemorrhage and one observational post-authorisation safety study (PASS, acquired fibrinogen deficiency part).

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.
- FGT1-0505 Study 505 was a prospective, open-label, non-controlled, multicentre phase II study evaluating the clinical and biological efficacy and safety of a single infusion of 3g of FGTW (fibrinogen concentrate) in patients with early post-partum haemorrhage.

  Sixteen patients were included: there were 8 successes, 1 partial success and 3 treatment failures in 12 evaluable patients. The investigator’s assessment of the FGTW efficacy in stopping haemorrhage was rated as excellent or good in 75% of patients.
- The 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 deficiency.

  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.

One hundred and fifty-six patients were included in the acquired deficiency part among which:

- Fifty-nine and thirty patients were respectively treated for PPH and trauma as leading causes of bleeding. Fewer patients were treated for other causes: twenty-three patients for cardiovascular surgeries, thirteen patients for liver/cirrhosis, six patients for gynaecological/obstetrical and twenty-one patients for various origins of deficiency in fibrinogen.
- One hundred and forty-four patients received CLOTTAFACT as a treatment; six patients as a prophylaxis (or prevention) and six patients received both a treatment and a prophylactic dose of CLOTTAFACT. A total of 178 bleeding episodes occurred in 156 patients. The total number of infusions was 169 as some patients received only 1 infusion to treat several concomitant haemorrhagic episodes. The mean dose administered per patient was 3.81 ± 2.93 g with a median dose of 3.00 g ranging from 1.50 to 4.50 g.
- The investigator's assessment of CLOTTAFACT efficacy in stopping haemorrhage was rated as excellent in 73.8% of patients.

Please also refer to the Swissmedic's approved "Arzneimittelinformation".

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 CLOTTAFACT.

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 CLOTTAFACT 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 CLOTTAFACT 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 CLOTTAFACT.

It is not anticipated that treatment with CLOTTAFACT 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 CLOTTAFACT.

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

Summary of safety concerns

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.	See Swiss SmPC (Fachinformation) “Warnings and precautions” and “Undesirable Effects”
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.	See Swiss SmPC (Fachinformation) “Warnings and precautions” and “Undesirable Effects”

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Severe hepatic impairment	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). Patients who are regularly treated with fibrinogen should receive appropriate vaccinations (hepatitis A and B).

Missing information

Risk	What is known
Severe hepatic impairment	Patients with severe hepatic impairment were not included in interventional clinical trials There was no signal, from preclinical studies, indicating that the liver could be a target organ for Clottafact and there are no hepatic risks anticipated with human fibrinogen products. Evaluation of clinical data did not reveal any potential hepatic risk associated with Clottafact.
Severe renal impairment	Patients with severe renal impairment were not included in interventional clinical trials There was no signal from preclinical studies indicating that the kidney could be a target organ for Clottafact 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 Clottafact. It is not anticipated that treatment with Clottafact could have kidney implications in the target population.
Pregnant and lactating women	The safety of human fibrinogen has not been evaluated in controlled clinical trials during pregnancy and breastfeeding. However, clinical experience in the treatment of obstetric complications does not suggest that any adverse effects should be expected on the course of the pregnancy or on the development of the foetus or the neonate.

Summary of risk minimisation measures by safety concern

Summary of Product Characteristics (SmPC) of CLOTTAFACT provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. The measures in the Swiss SmPC (Fachinformation) are known as routine risk minimisation measures.

CLOTTAFACT has no additional risk minimisation measures.

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.

Summary of changes to the Risk Management Plan over time

Not applicable.