VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Fibryga is used for the treatment and prophylaxis of bleeding, including of bleeding during surgery, in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency.

Fibrinogen deficiency is a bleeding disorder that is caused by the lack of fibrinogen, which is one of the proteins involved in the blood coagulation (clotting) process. Patients with congenital fibrinogen deficiency are more prone to bleeding than normal and have prolonged bleeding. Congenital fibrinogen deficiency is caused by a defective gene on chromosome 4.

Congenital fibrinogen deficiency may occur in all races and ethnic groups. However, higher incidences are observed in countries where consanguineous marriages are practiced, such as in the Middle East and Southern India. It is estimated that 1 - 2 per million children in the general western population are born with congenital fibrinogen deficiency.

VI.2.2 Summary of treatment benefits

Fibryga contains the active substance fibrinogen, which replaces the missing fibrinogen in patients who do not have sufficient levels of fibrinogen in their blood. So far, data on efficacy and safety is available from two clinical studies involving 35 patients, the first study being completed and the second study ongoing.

In these studies, the medicine has been shown to be efficacious in helping to stop bleeding and in preventing bleeding in patients with fibrinogen deficiency. In fact, Fibryga was demonstrated to be efficacious in all bleeding episodes and in surgical prophylaxis.

Based on the results of both studies it can be concluded that Fibryga is efficacious and has a good safety profile in its proposed indication for prophylaxis and treatment of patients with congenital fibrinogen deficiency. One additional study is ongoing to further investigate the efficacy and safety of Fibryga in children.

VI.2.3 Unknowns relating to treatment benefits

There is no experience using Fibryga in pregnant or breastfeeding women, the elderly population, and patients with an impaired function of the liver.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic (hypersensitivity) reactions, including severe, sudden allergic	True hypersensitivity reactions are rare but – as with any other product - allergic type hypersensitivity reactions to	Healthcare professionals should ask patients to watch out for early signs of hypersensitivity reactions including hives, generalised urticaria

Risk	What is known	Preventability
(anaphylactic) reactions	human fibrinogen may occur. The outcome of such reactions depends on their severity. While severe anaphylactic reactions can be life threatening, patients with allergic reactions usually recover following treatment.	(itchy rash), tightness of the chest, wheezing, hypotension (low blood pressure) or anaphylaxis (when any or all of the above symptoms develop rapidly and are intense). If signs or symptoms of hypersensitivity occur, patients should be advised to stop using Fibryga immediately and contact their physician. Patients who are likely to develop hypersensitivity or allergic reactions may be pre-treated with corticosteroids and/or antihistamines.
Blood clots (Thromboembolic events)	Blood clots may affect the arteries or veins. In the veins this may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots may occur in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries. Known risk factors for thromboembolic events (blood clots) include: advanced age, immobility, (major) surgery, obesity, multiple trauma, hip fracture, lower extremity paralysis caused by spinal cord injury, cardiac or respiratory failure, presence of central venous lines, oestrogens, and a wide variety of inherited and acquired haematological conditions. These events may also occur in: congenital fibrinogen deficiency without fibrinogen concentrate administration, neonates, peri- or postoperative patients.	Healthcare professionals should monitor patients at risk who receive Fibryga for signs and symptoms of thrombosis. Where appropriate preventive anti-thrombotic medicines may be given.

Important potential risks

Risk	What is known
Virus safety (Transmission of infectious agents)	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 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), 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 (infection of the unborn baby) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or abnormal breakdown of red blood cells).

Missing information

Risk	What is known
Safety in elderly patients	The safety of Fibryga in elderly patients has not been established in controlled clinical trials.
Safety in pregnant or breast feeding women	The safety of Fibryga for use in pregnant or breast feeding women has not been established in controlled clinical trials.
Safety in patients with an impaired function of the liver (hepatic impairment)	The safety Fibryga in patients with an impaired function of the liver has not been established in controlled clinical trials.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC; locally authorised prescribing information) which 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 prescribing information 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.

The Summary of Product Characteristics and the Package Leaflet for Fibryga can be found on the homepage of national health authorities where Fibryga is approved.

VI.2.6 Planned post-authorisation development plan

Study/activity	Objectives	Safety concern/efficacy issue addressed	Status	Date for submission of interim or final reports
None	Not applicable	Not applicable	Not applicable	Not applicable

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

Version	Date	Safety Concerns	Comment
02	30-Dec-2016	**Identified risks** - Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events **Potential risks** - Suspected transmission of infectious agents **Missing information** - Safety in elderly patients - Safety in pregnant or breast feeding women - Safety in patients with hepatic impairment	Update of RMP according to RMS Day 70 assessment report from PEI and CMS Day 100 comments within procedure DE/H/4900/001/DC. Minor changes in wording of the indication concerning patients with congenital hypo-, dys- or afibrinogenaemia were introduced in Part I, Module SI.1 and Module SIII.1. Changes in the description of the posology, the method of administration and the pharmaceutical forms and strengths were introduced in Part I. Among others: - The recommendation to administer 70 mg per kg of body weight in case of the patient's fibrinogen level should be unknown for treatment of bleeding was deleted. - A description of the treatment of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia was added. A comment concerning the risk of Fibryga for thromboembolic events compared to similar products was added in Module SVII. A description of the Octapharma Pharmacovigilance plan was added in Part III. The quarterly signal analysis was included as routine PV activity for all risks in Part III.1. The studies FORMA-02 and

			FORMA-04 were removed from Sections III.4.3 and III.5 since these studies were not requested by any health authority to address particular safety concerns. Skin reactions and thrombophlebitis were added as undesirable effects in Part V.I. Section VI.2.4 was updated to correctly reflect the classification of the included risks.
01	03-May-2016	**Identified risks** - Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events **Potential risks** - Suspected transmission of infectious agents **Missing information** - Safety in elderly patients - Safety in pregnant or breast feeding women - Safety in patients with hepatic impairment	First edition of the RMP