VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Haemophilia is a rare inherited bleeding disorder primarily expressed in males, which prevents individuals from producing normal levels of clotting at the site of a wound or injury. Haemophilia A, the most common form, occurs globally in 20 out of 100,000 male births. Haemophilia B occurs less commonly with a frequency of 3 to 4 cases out of 100,000 male births. Haemophilia disorder can also be acquired later in life with an estimated rate of 1 to 4 individuals per million each year. Prior to the introduction of safer blood products and more effective treatments, the life expectancy of individuals with haemophilia was very low (<30 years old) with hemorrhage as the most common cause of death. However, patients now experience a higher quality of life, with patient survival closer to the general male population. Yet, serious complications may still occur in patients with the development of inhibitors (antibodies) to clotting factor, which make individuals more prone to uncontrolled bleeding. As many as one-third of previously untreated patients with severe or moderately severe haemophilia A are at risk for developing inhibitors. In individuals with haemophilia B, inhibitor development occurs less frequently at a rate of 1% to 3%. FEIBA, which is a concentrated therapy of clotting factors, may be used to promote clotting and manage bleeding episodes in haemophilia patients with inhibitors. This therapy can be used to treat and prevent bleeding in patients

born with haemophilia A and haemophilia B who have developed inhibitors. FEIBA is also used as a preventive therapy in haemophilia A patients who are at high risk of severe bleeds. Additionally, the therapy may treat individuals with acquired factor VIII inhibitors. The successful activation of clot formation in inhibitor patients promotes the reduction or elimination of bleeds, which may improve overall patient survival and quality of life.

VI.2.2 Summary of Treatment Benefits

Control of acute bleeding episodes

In a study involving 49 subjects with 165 mild or moderate bleeding episodes, 93% responded within 3 days: 36% by 1 infusion within 12 hours, 42% by ≥ 1 infusion within 36 hours, and 14% within 72 hours.

In a prospective study in France, 77 subjects were surveyed. The efficacy was judged by the physician and the subject as good or excellent in 86.4% of bleeding episodes, poor in 13.1%, and non-existent in 0.4%.

A retrospective, multicenter study of 60 hemophilia subjects who received FEIBA between 1978 and 1993. The efficacy of FEIBA was considered excellent or good for 81.3% of bleeding episodes, poor for 16.9%, and uncontrolled for 1.8%.

Another study involved 41 hemophilia subjects with FVIII or FIX inhibitors who experienced 106 evaluable bleeding episodes treated with FEIBA VH.

Eighty-eight percent were controlled (78% with up to 3 infusions in 36 hours and 10% with > 1 infusion in > 36 hours). Fifty-two percent of bleeding episodes were controlled with 1 infusion of FEIBA VH (48% in 12 hours and 4% in > 12 hours).

Control of bleeding during surgery

There were approximately 17 publications between 1997 and 2012 concerning the use of FEIBA for minor and major orthopedic and non-orthopedic surgery in hemophilic patients with FVIII inhibitors. The numbers of reported major and minor procedures were 61 and 138 respectively. The hemostatic outcome was rated as ‘excellent’ or ‘good’ in 78–100% of major cases and 75–100% of minor cases.

Conclusions on the treatment of bleeding episodes in the FEIBA Prophylaxis study

FEIBA prophylaxis study (090701), hemostatic efficacy (excellent, good, fair, none, not done) and the number of infusions (1, 2, 3, ≥ 4 infusions) used to treat a bleeding

episodes were assessed in the on-demand arm and prophylaxis arm. Only the on-demand arm will be summarized. The hemostatic efficacy of FEIBA in the treatment of bleeding episodes was rated excellent or good in 90.2% of subjects at 24 ± 1 h post-infusion. Furthermore, the percentage of bleeding episodes treated with 1-2, 3 or ≥4 bleeds was 78%, 10%, and 12%, respectively.

VI.2.3 Unknowns relating to Treatment Benefits

The applicability of the efficacy of FEIBA in all patients in the target population is likely to be the same.

The clinical and post-marketing experiences with FEIBA are effective in controlling bleeding in subjects with Factor VIII or Factor IX inhibitors. There is no relationship between efficacy and inhibitor titre.

The results of both clinical and published studies were comparable between patients, whatever their initial diagnosis was congenital haemophilia A and inhibitors, congenital haemophilia B and inhibitors or acquired haemophilia.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Allergic type- hypersensitivity reactions (Allergic reactions)	An allergic reaction can occur from one of the components of FEIBA. On rare occasion, severe hypersensitivity reactions may progress to allergic reactions resulting in shock.	Monitoring for early symptoms of allergic reaction.
Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke) (Blood clots)	These may affect the arteries or veins. In the veins this may lead to blood clots in the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots 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. DIC is a blood clot disorder due to a disturbed ratio between the consumption and production of blood platelets and blood clotting factors.	The use of anti-thrombotic medicines and heparin.
Insufficient response to bypassing agents	Due to patient-specific factors, the response to a bypassing agent	To date, no laboratory test has been validated to monitor the

Risk	What is Known	Preventability
	can vary, and in a given bleeding situation patients experiencing insufficient response to one agent may respond to another.	biological effects or predict the outcome of treatment of bypassing agents.
Passive transfer of hepatitis B surface antibodies	After administration of high doses of FEIBA, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.	Provider's awareness of the passive transfer of antibodies will prevent incorrect interpretation of laboratory results.

Important Potential Risks

Risk	What is known
Transmission of Infectious Agents	When medicines are prepared from human blood or plasma, the possibility of passing on infection cannot be totally excluded. This also applies to unknown or emerging viruses or other types of infections.
Improper self-administration	There is the potential for incorrect dosing during prophylaxis where the individual patient is maintained on an insufficient dose, resulting in choosing the incorrect route of administration, incorrect rate, or incorrect dose which may lead to underdose or overdose and subsequently insufficient effects or bleeding. Any 'breakthrough bleeding' is undesirable, but not necessarily avoidable.
Inadvertent administration of the incorrect dose or concentration of FEIBA	As with any medication, there is the potential for human error. There are currently two pack sizes of FEIBA on the market (500 U and 1000 U) and one proposed pack size (2500 U). There is the potential for use of the incorrect pack size of FEIBA. Further, there are currently two concentrations of FEIBA on the market: 25 U/ml (500 U pack size) and 50 U/ml (1000 U pack size). The proposed 2500 U pack size will also have a 50 U/ml concentration. Therefore, there is the potential for inadvertent administration of the incorrect concentration of FEIBA. There have been no reports of medication errors related to use of the incorrect dose or concentration of FEIBA in the US, where the 2500 U pack size has been on the market since April 2012.

Missing Information

Risk	What is known
Insufficient data in children under 6 years of age	Children younger than 6 years of age were included in clinical trials of the product; however, the number of such children is limited. A review of medical literature for FEIBA identified 13 children under the age of 6 for whom age can be verified:

Risk	What is known
	• Sjamsoedin 1981, 3 patients • Hilgartner 2003, 3 patients • Lambert 2006, 1 patient • Kraut 2007, 5 patients • Leissinger 2007, 1 patient.
Prophylactic use in hemophilia B patients with inhibitors	The experience in hemophilia B patients with factor IX inhibitors is limited due to the rarity of the disease.
Insufficient data in pregnant and lactating women	The prescribing physician will decide if FEIBA may be used during pregnancy and breast-feeding. Due to the increased risk of thrombosis during pregnancy, FEIBA should be administered only under careful medical monitoring and only if absolutely necessary.
Insufficient data in geriatric patients	The experience in geriatric patients is limited; the prescribing physician should make a benefit/risk assessment prior to administration of FEIBA

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

There are no additional risk minimization measures for FEIBA.

VI.2.6. Planned Post Authorization Development Plan

There are no planned post-authorization studies in the development plan.

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

Version	Date	Safety Concerns	Comment
1.0	20 June 2001	**Identified Risks** • Hypersensitivity • Disseminated Intravascular Coagulation (DIC) • Poorly defined best practices for prophylactic regimens for haemophilia A **Potential Risks** • Viral Transmission **Missing information** • none	none
2.0	23 July 2007	**Identified Risks** • Hypersensitivity • Disseminated Intravascular Coagulation (DIC) • Poorly defined best practices for prophylactic regimens for haemophilia A **Potential Risks** • Viral Transmission **Missing information** • There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, case studies have shown the successful use of FEIBA in the young age group. • Poorly defined best practice for prophylactic regimens for haemophilia A	none
3.0	22 August 2007	**Identified Risks** • Hypersensitivity • Disseminated Intravascular Coagulation (DIC) • Poorly defined best practices for	none

Version	Date	Safety Concerns	Comment
		prophylactic regimens for haemophilia A **Potential Risks** • Viral Transmission **Missing information** • There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, case studies have shown the successful use of FEIBA in the young age group. • Poorly defined best practice for prophylactic regimens for haemophilia A	
4.0	25 March 2009	**Identified Risks** • Hypersensitivity to active substance • Disseminated Intravascular Coagulation (DIC) **Potential Risks** • Viral Transmission **Missing information** • There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, case studies have shown the successful use of FEIBA in the young age group. • Poorly defined best practice for prophylactic regimens for haemophilia A	none
5.0	21 December 2009	**Identified Risks** • Hypersensitivity to active substance • Disseminated Intravascular Coagulation (DIC) • Poorly defined best practices for prophylactic regimens for haemophilia A **Potential Risks** • Viral Transmission • Improper self-administration **Missing information** • There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, case studies have shown	none

Version	Date	Safety Concerns	Comment
		the successful use of FEIBA in the young age group. • Poorly defined best practice for prophylactic regimens for haemophilia A	
6.0	17 October 2012	**Identified Risks** • Allergic type- hypersensitivity reaction • Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke) • Insufficient response to bypassing agents **Potential Risks** • Transmission of Infection Agents • Improper self-administration **Missing information** • There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, case studies have shown the successful use of FEIBA in the young age group. • Poorly defined best practice for prophylactic regimens for haemophilia A	none
7.0	29 May 2013	**Identified Risks** • Allergic type- hypersensitivity reaction • Thrombotic and thromboembolic events • Insufficient response to bypassing agents • Passive transfer of hepatitis B surface antibodies **Potential Risks** • Transmission of Infection Agents • Improper self-administration **Missing information** • Insufficient data in children under 6 years of age	None

Version	Date	Safety Concerns	Comment
7.0 Update	29 October 2013	The potential risk of Inadvertent administration of the incorrect dose or concentration of FEIBA was added. For the risk of Inadvertent administration of the incorrect dose or concentration of FEIBA, additional risk minimization in the form of a DHPC was added.	RMP update based on Irish Medicines Board and AGES assessments during the MRP variation
8.0	11 August 2014	**Identified Risks** • Allergic type – hypersensitivity reactions • Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke) • Insufficient response to bypassing agents • Passive transfer of hepatitis B surface antibodies **Potential Risks** • Transmission of Infectious Agents • Improper self-administration • Inadvertent administration of the incorrect dose or concentration of FEIBA **Missing Information** • Insufficient data in children under 6 years of age • Prophylactic use in hemophilia B patients with inhibitors • Insufficient clinical data on use in pregnancy and lactation • Insufficient clinical data on use in geriatric patients	RMP update based on the MRP variation AT/H/0343/001-002/IB/021 and missing information update (insufficient clinical data in pregnant/lactating women and geriatric patients) was included based on assessment of current clinical data.

Part VII: Annexes

Annexes

1	EudraVigilance Interface
2	SmPC & Package Leaflet
3	Worldwide Marketing Authorization by Country (including EEA)
4	Synopsis of On-Going and Completed Clinical Trial Program
5	Synopsis of On-Going and Completed Pharmacoepidemiological Study Program
6	Protocols for Proposed and On-Going Studies in Categories 1-3 of the Section "Summary Table of Additional Pharmacovigilance Activities" In RMP Part III
7	Specific Adverse Event Follow-Up Forms
8	Protocols for Proposed and On-Going Studies in RMP Part IV
9	Newly Available Study Reports for RMP Parts III & IV
10	Details of Proposed Additional Risk Minimization Measures
11	Mock-Up of Proposed Additional Risk Minimization Measures
12	Other Supporting Data (including referenced material)