Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

FEIBA 50 U/ml powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Factor VIII Inhibitor Bypassing Activity

1 ml contains 50 U* factor VIII inhibitor bypassing activity.

FEIBA 50 U/ml is available in three different presentations:

- The presentation 500 U FEIBA contains 500 U factor VIII inhibitor bypassing activity in 200 – 600 mg human plasma protein.
- The presentation 1 000 U FEIBA contains 1 000 U factor VIII inhibitor bypassing activity in 400 – 1 200 mg human plasma protein.
- The presentation 2 500 U FEIBA contains 2 500 U factor VIII inhibitor bypassing activity in 1 000 – 3 000 mg human plasma protein.

FEIBA also contains the factors II, IX and X, mainly in non-activated form, as well as activated factor VII. Factor VIII coagulation antigen (FVIII C:Ag) is present at a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present in trace amounts only, if at all.

* 1 unit of FEIBA shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma by 50 % of the buffer value (blank value).

Excipient with known effect:

500 U
FEIBA contains approximately 40 mg sodium per vial.

1 000 U
FEIBA contains approximately 80 mg sodium per vial.

2 500 U
FEIBA contains approximately 200 mg sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

White, off-white or pale green powder.The pH value of the ready-to-use solution is between 6.8 and 7.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment and prophylaxis of bleeding in haemophilia A patients with inhibitors.
- Treatment of bleeding in haemophilia B patients with inhibitors.
- Treatment and prophylaxis of bleeding in non-haemophiliacs with acquired inhibitors to factor VIII.
- Prophylaxis in surgical interventions in haemophilia A patients with inhibitors.

FEIBA can be used for all age groups.

4.2 Posology and method of administration

The treatment is to be initiated and monitored by a physician experienced in the treatment of coagulation disorders.

Posology

Dosage and duration of treatment depend on the severity of the haemostatic disorder, the localization and the extent of the bleeding, as well as the clinical condition of the patient.

Dosage and frequency of administration should always be guided by the clinical efficacy in each individual case.

As a general guideline, a dose of 50 – 100 U FEIBA per kg body weight is recommended; a single dose of 100 U/kg body weight and a maximum daily dose of 200 U/kg body weight must not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. See section 4.4.

Paediatric population

The experience in children under 6 years of age is limited; the same dose regimen as in adults should be adapted to the child's clinical condition.

1) Spontaneous bleeding

Joint, muscle and soft tissue haemorrhage
A dose of 50 – 75 U/kg body weight at 12-hour intervals is recommended for minor to moderately severe bleeding. The treatment is to be continued until a clear improvement of the clinical symptoms, e.g. reduction of pain, decrease of swelling or increase of joint mobility, occurs.

For severe muscle and soft tissue bleeding, e.g. retroperitoneal haemorrhages, a dose of 100 U/kg body weight at 12-hour intervals is recommended.

Mucous membrane haemorrhage
A dose of 50 U/kg body weight every 6 hours under careful monitoring of the patient (visual control of bleeding, repeated determination of haematocrit) is recommended. If the bleeding does not stop, the dose may be increased to 100 U/kg body weight, however a daily dose of 200 U/kg body weight must not be exceeded.

Other severe haemorrhages
In severe haemorrhage, such as CNS bleeding, a dose of 100 U/kg body weight at 12-hour intervals is recommended. In individual cases, FEIBA may be administered at 6-hour intervals, until clear improvement of the clinical condition is achieved (The maximum daily dose of 200 U/kg body weight must not be exceeded!).

2) Surgery

In surgical interventions, an initial dose of 100 U/kg body weight may be administered preoperatively, and a further dose of 50 – 100 U/kg body weight may be administered after 6 – 12 hours. As a postoperative maintenance dose, 50 – 100 U/kg body weight may be administered at 6 – 12-hour intervals; dosage, dosage intervals and duration of the peri- and postoperative therapy are guided by the surgical intervention, the patient's general condition and the clinical efficacy in each individual case (The maximum daily dose of 200 U/kg body weight must not be exceeded!).

3) Prophylaxis in haemophilia A patients with inhibitors

Prophylaxis of bleeding in patients with a high inhibitor titre and frequent haemorrhages after failed immune tolerance induction (ITI) or when an ITI is not considered:
A dose of 70 – 100 U/kg body weight every other day is recommended. If necessary, the dose may be increased to 100 U/kg body weight per day or it may be decreased gradually.

Prophylaxis of bleeding in patients with a high inhibitor titre during an immune tolerance induction (ITI):

FEIBA may be administered concomitantly with factor VIII administration, in a dosage range of 50 – 100 U/kg body weight, twice per day, until the factor VIII inhibitor titre has decreased to < 2 B.U.*

* 1 Bethesda Unit is defined as the amount of antibodies which inhibits 50 % factor VIII activity in incubated plasma (2 h at 37 °C).

4) Use of FEIBA in special patient groups

See section 5.1 for information in relation to haemophilia B patients with factor IX inhibitor.

In combination with factor VIII concentrate, FEIBA was also used for long term therapy to achieve complete and permanent elimination of the factor VIII inhibitor.

Monitoring

In case of inadequate response to treatment with the product, it is recommended that a platelet count be performed because a sufficient number of functionally intact platelets are considered to be necessary for the efficacy of the product.

Due to the complex mechanism of action, no direct monitoring of active ingredients is available. Coagulation tests such as the whole blood coagulation time (WBCT), the thromboelastogram (TEG, r-value) and the aPTT usually show only little reduction and do not necessarily correlate with the clinical efficacy. Therefore, these tests have little significance in the monitoring of the therapy with FEIBA. See section 4.4.

Method of administration

Slowly infuse via the intravenous route. An infusion rate of 2 U/kg body weight per minute must not be exceeded.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

FEIBA must not be used in the following situations if therapeutic alternatives to FEIBA are available:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Disseminated Intravascular Coagulation (DIC).
- Acute thrombosis or embolism (including myocardial infarction).

See section 4.4.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

WARNINGS

Hypersensitivity Reactions
FEIBA can precipitate allergic-type hypersensitivity reactions that have included urticaria, angioedema, gastrointestinal manifestations, bronchospasm and hypotension; these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia and hypertension have also been reported.

Patients should be informed of the early signs of hypersensitivity reactions, for example erythema, skin rash, generalized urticaria, pruritus, breathing difficulties/dyspnoea, tightness of the chest, general indisposition, dizziness and drop in blood pressure up to allergic shock.

At the first sign or symptom of an infusion/hypersensitivity reaction, FEIBA administration should be stopped and medical care initiated as appropriate.

When considering re-exposure to FEIBA in patients with suspected hypersensitivity to the product or any of its components, the expected benefit and the risk of re-exposure must be carefully weighed, taking into account the known or suspected type of the patient's hypersensitivity (allergic or non-allergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.

Thrombotic and Thromboembolic Events

Thrombotic and thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction and stroke, have occurred in the course of treatment with FEIBA.

Some of these events occurred with doses above 200 U/kg/day or in patients with other risk factors (including DIC, advanced atherosclerotic disease, crush injury or septicaemia) for thromboembolic events. Concomitant treatment with recombinant Factor VIIa (rFVIIa) likely increases the risk of developing a thromboembolic event. The risk of thrombotic and thromboembolic events may be increased with high doses of FEIBA. The possible presence of such risk factors should always be considered in patients with congenital and acquired haemophilia.

FEIBA should be used with particular caution and only if there are no therapeutic alternatives in patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, DIC, arterial or venous thrombosis, post-operative immobilization, elderly patients and neonates.

Thrombotic microangiopathy (TMA) has not been reported in FEIBA clinical studies. Cases of TMAs were reported in an emicizumab clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding. The safety and efficacy of FEIBA for breakthrough bleeding in patients receiving emicizumab has not been established. Therefore, benefit-risk evaluation of FEIBA to be administered to emicizumab exposed patients is required, and patients must be closely monitored by their physicians (see also section 4.5).

If signs or symptoms of thrombotic and thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. When used to stop bleeding, the product should be given only for as long as absolutely necessary to achieve the therapeutic goal.

Therapy monitoring

Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients receiving 100 U/kg body weight or more must be monitored carefully, particularly for the development of DIC and/or acute coronary ischaemia and for symptoms of other thrombotic or thromboembolic events. High doses of FEIBA should be administered only as long as strictly necessary in order to stop a haemorrhage.

If clinically significant changes in blood pressure or pulse rate, respiratory distress, coughing or chest pain occur, the infusion is to be discontinued immediately and appropriate diagnostic and therapeutic measures are to be initiated. Significant laboratory parameters for DIC are a drop in fibrinogen, a drop of the thrombocyte count and/or the presence of fibrin/fibrinogen degradation products (FDP). Other parameters for DIC are a clearly prolonged thrombin time, prothrombin time or aPTT. In patients with inhibitor haemophilia or with acquired inhibitors to factors VIII, IX and/or XI, the aPTT is prolonged by the underlying disease.

Patients with inhibitor haemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA, may have increased bleeding tendency as well as increased risk of thrombosis at the same time.

Laboratory tests and clinical efficacy

In vitro tests, such as aPTT, whole blood coagulation time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalize these values by increasing the dose of FEIBA cannot be successful, and are even to be strongly rejected because of the possible risk of triggering a DIC through overdosing.

Significance of the thrombocyte count

If the response to treatment with FEIBA is inadequate, conducting a thrombocyte count is recommended since a sufficient number of functionally intact thrombocytes is necessary for the efficacy of FEIBA.

PRECAUTIONS

Thrombotic and Thromboembolic Complications
In the following situations, FEIBA is to be applied only if no reaction to treatment with suitable blood coagulation factor concentrates can be expected – e.g. in case of a high inhibitor titre and a life-threatening haemorrhage or risk of bleeding (e.g. post-traumatically or postoperatively):

- Disseminated intravascular coagulation (DIC): laboratory findings and/or clinical symptoms.
- Liver damage: Due to the delayed clearance of activated coagulation factors, patients with impaired liver function are at increased risk of developing DIC.
- Coronary heart disease, acute thrombosis and/or embolism.

Patients who receive FEIBA should be monitored for the development of DIC, acute coronary ischaemia, and signs and symptoms of other thrombotic or thromboembolic events. At the first signs or symptoms of thrombotic and thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

Discordant Response to Bypassing Agents
Due to patient-specific factors the response to a bypassing agent can vary, and in a given bleeding situation patients experiencing insufficient response to one agent may respond to another agent. In case of insufficient response to one bypassing agent, use of another agent should be considered.

Anamnestic Responses
Administration of FEIBA to patients with inhibitors may result in an initial "anamnestic" rise in inhibitor levels. Upon continued administration of FEIBA, inhibitors may decrease over time. Clinical and published data suggest that the efficacy of FEIBA is not reduced.

Interference with Laboratory Tests
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.

FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

Paediatric population
Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age. The same dose regimen as in adults should be adapted to the child's clinical condition.

Elderly
There are only limited clinical trial data with the use of FEIBA in elderly patients.

Prophylactic use in haemophilia B patients with inhibitors
Due to the rarity of the disease, only limited clinical data is available for the prophylaxis of bleeding in haemophilia B patients (literature case reports, n = 6, clinical data in prophylaxis study 090701, n = 1, and PASS-EU-006, n = 1).

Transmission of infectious agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. 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 with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived products including FEIBA.

Sodium
500 U
FEIBA contains approximately 40 mg sodium per vial, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

1 000 U
FEIBA contains approximately 80 mg sodium per vial, equivalent to 4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

2 500 U
FEIBA contains approximately 200 mg sodium per vial, equivalent to 10 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No adequate and well-controlled studies of the combined or sequential use of FEIBA and recombinant Factor VIIa, antifibrinolytics or emicizumab have been conducted.

The possibility of thromboembolic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA. In cases of concomitant rFVIIa use a potential drug interaction cannot be excluded according to available *in vitro* data and clinical observations (potentially resulting in adverse events such as a thromboembolic event).

During two emicizumab clinical trials, 23 participants receiving emicizumab prophylaxis also received FEIBA for the management of 78 breakthrough bleeds. 59 of the 78 bleeds were managed with an average daily dose ≤ 100 U/kg/day for ≤ 2 days without TMA complications. 19 of the 78 bleeds were managed with > 100 U/kg/day for > 1 day with TMA complication occurring in 3 patients (of whom 2 patients also received rFVIIa for the same bleeding event). See section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of FEIBA in pregnant women. Physicians should balance the potential risks and only prescribe FEIBA if clearly needed, taking into consideration that pregnancy confers an increased risk of thromboembolic events, and several complications of pregnancy that are associated with an increased risk of DIC.

Breastfeeding
There are no adequate data from the use of FEIBA in lactating women. The coagulation factors are large protein molecules; therefore, the amount in breast milk is likely to be very low. However, as no data is available, physicians should balance the potential risks and only prescribe FEIBA if clearly needed, taking into consideration that the postpartum period confers an increased risk of thromboembolic events.

Fertility
No animal reproduction studies have been conducted with FEIBA, and the effects of FEIBA on fertility have not been established in controlled clinical trials.
See section 4.4 for information on parvovirus B19 infection.

4.7 Effects on ability to drive and use machines

FEIBA has no, or negligible, influence on the ability to drive or to use machines.

4.8 Undesirable effects

FEIBA can precipitate allergic-type hypersensitivity reactions that have included urticaria, angioedema, gastrointestinal manifestations, bronchospasm and a drop in blood pressure; these reactions can be severe and can be systemic (e.g.,

anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). See also section 4.4 Hypersensitivity Reactions.

The adverse reactions presented in this section have been reported from post marketing surveillance as well as from studies with FEIBA for the treatment of bleeding episodes in paediatric and adult patients with haemophilia A or B and inhibitors to factors VIII or IX. One study also enrolled acquired haemophilia patients with factor VIII inhibitors (2 of 49 patients). The adverse reactions from a third study comparing prophylaxis with on-demand treatment have been added.

Frequency categories are defined according to the following convention:
very common ≥ 1/10
common ≥ 1/100 to < 1/10
uncommon ≥ 1/1 000 to < 1/100
rare ≥ 1/10 000 to < 1/1 000
very rare < 1/10 000
unknown cannot be estimated from the available data

Adverse Reactions		
System organ class (SOC)	**Preferred current MedDRA Term**	**Frequency* Category**
Blood and lymphatic system disorders	Disseminated intravascular coagulation (DIC)	Unknown
	Increase of inhibitor titre (anamnestic response)[a]	Unknown
Immune system disorders	Hypersensitivity[c]	Common
	Urticaria	Unknown
	Anaphylactic reaction	Unknown
Nervous system disorders	Paraesthesia	Unknown
	Hypaesthesia	Unknown
	Thrombotic stroke	Unknown
	Embolic stroke	Unknown
	Headache[c]	Common
	Somnolence	Unknown
	Dizziness[b]	Common
	Dysgeusia	Unknown
Cardiac disorders	Cardiac infarction	Unknown
	Tachycardia	Unknown
Vascular disorders	Thrombosis	Unknown
	Venous thrombosis	Unknown
	Arterial thrombosis	Unknown
	Embolism (thromboembolic complications)	Unknown
	Hypotension[c]	Common
	Hypertension	Unknown
	Flushing	Unknown
Respiratory, Thoracic, and Mediastinal disorders	Pulmonary embolism	Unknown
	Bronchospasm	Unknown
	Wheezing	Unknown
	Cough	Unknown
	Dyspnoea	Unknown
Gastrointestinal disorders	Vomiting	Unknown
	Diarrhoea	Unknown
	Abdominal discomfort	Unknown
	Nausea	Unknown
Skin and subcutaneous tissue disorders	Sensation of numbness in the face	Unknown
	Angioedema	Unknown
	Urticaria	Unknown
	Pruritus	Unknown
	Rash[c]	Common
General disorders and administration site conditions	Pain at the injection site	Unknown
	Malaise	Unknown
	Feeling hot	Unknown
	Chills	Unknown

	Pyrexia Chest pain Chest discomfort	Unknown Unknown Unknown
Investigations	Drop in blood pressure Hepatitis B surface antibody positive[c] Fibrin D-dimer increased	Unknown Common Unknown

[*] A precise estimate of the rate of these adverse reactions is not possible from the available data.
[a] Increase of inhibitor titre (anamnestic response) [not a MedDRA PT] is the rise of previously existing inhibitor titres occurring after the administration of FEIBA. See section 4.4.
[b] ADR reported in the original and prophylaxis studies. Frequency shown is from the prophylaxis study only.
[c] ADR reported in the prophylaxis study. Frequency shown is from the prophylaxis study.

Class Reactions

Other symptoms of hypersensitivity reactions to plasma-derived products include lethargy and restlessness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The risk of thrombotic and thromboembolic events (including DIC, myocardial infarction, venous thrombosis, and pulmonary embolism) may be increased with high doses of FEIBA. Some of the reported thromboembolic events occurred with doses above 200 U/kg or with patients with other risk factors for thromboembolic events. If signs or symptoms of thrombotic and thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated. See Section 4.4.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors, ATC code: B02BD03.

Although FEIBA was developed in the early seventies and its factor VIII inhibitor bypassing activity has been proven *in vitro* as well as *in vivo*, its mode of action is still the subject of scientific discussion. FEIBA, as found with activity assays, is composed of prothrombin complex zymogens which are both procoagulant (prothrombin, FVII, FIX, FX) and anticoagulant (protein C) in relatively equal quantities to the arbitrary FEIBA potency unit but its procoagulant enzyme content is relatively low. FEIBA, thus, contains the proenzymes of the prothrombin complex factors, but only very small amounts of their activation products, with the contents of FVIIa being the highest.

Current scientific works point to the role of specific components of the activated prothrombin complex, prothrombin (FII) and activated factor X (FXa) in the mode of action of FEIBA.

FEIBA controls bleeding by induction and facilitation of thrombin generation, a process for which the formation of the prothrombinase-complex is crucial. A number of biochemical *in vitro* and *in vivo* studies have shown that FXa and prothrombin play a critical role in the activity of FEIBA. The prothrombinase complex has been found to be a major target site for FEIBA. Apart from prothrombin and FXa, FEIBA contains other proteins of the prothrombin complex, which could also facilitate haemostasis in haemophilia patients with inhibitors.

Treatment of haemophilia B patients with inhibitors

The experience in haemophilia B patients with factor IX inhibitors is limited due to the rarity of the disease. Five haemophilia B patients with inhibitors were treated with FEIBA during clinical trials either on-demand, prophylactically or for surgical interventions:

In a prospective open-label, randomized, parallel clinical study in haemophilia A or B patients with persistent high-titre inhibitors (090701, PROOF), 36 patients were randomized to either 12 months ± 14 days of prophylactic or on-demand therapy. The 17 patients in the prophylaxis arm received 85 ± 15 U/kg FEIBA administered every other day and the 19 patients in the on-demand arm were treated individually determined by the physician. Two haemophilia B patients with inhibitors were treated in the on-demand arm and one haemophilia B patient was treated in the prophylactic arm. The median ABR (annualized bleeding rate) for all types of bleeding episodes in patients in the prophylaxis arm (median ABR = 7.9) was less than that of patients in the on-demand arm (median ABR = 28.7), which amounts to a 72.5 % reduction in median ABRs between treatment arms.

In another completed prospective non-interventional surveillance study of the perioperative use of FEIBA (PASS-INT-003, SURF) a total of 34 surgical procedures were performed in 23 patients. The majority of patients (18) were congenital haemophilia A patients with inhibitors, two were haemophilia B patients with inhibitors and three were patients with acquired haemophilia A with inhibitors. The duration of FEIBA exposure ranged from 1 to 28 days, with a mean of 9 days and a median of 8 days. The mean cumulative dose was 88 347 U and the median dose was 59 000 U. For haemophilia B patients with inhibitors, the longest exposure to FEIBA was 21 days and the maximum dose applied was 7 324 U.

In addition, 48 patients in literature are reported when FEIBA was used for treatment and prevention of bleeding episodes in haemophilia B patients with factor IX inhibitor (34 haemophilia B patients with inhibitors were treated on-demand, six haemophilia B patients with inhibitors were treated prophylactically and eight haemophilia B patients with inhibitors were treated for surgical procedures).

There are also isolated reports on the use of FEIBA in the treatment of patients with acquired inhibitors to factors IX, X, XI and XIII.
In rare cases, FEIBA was also used in patients with the presence of von Willebrand factor inhibitor.

5.2 Pharmacokinetic properties

As the mode of action of FEIBA is still being discussed, it is not possible to make a conclusive statement about the pharmacokinetic properties.

5.3 Preclinical safety data

Based on acute toxicity studies in factor VIII knockout mice and in normal mice, and in rats, with doses higher than the maximum daily dose in humans (> 200 U/kg body weight), it can be concluded that the side effects in connection with FEIBA are mainly the result of hypercoagulation due to the pharmacological properties.

Toxicity studies with repeated administration in animal experiments are practically unfeasible as interference occurs through the development of antibodies to heterologous proteins.

Since human blood coagulation factors are not seen as carcinogenic or mutagenic, experimental animal studies, especially in heterologous species, were not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sodium chloride
Sodium citrate

Solvent: Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except the solvent mentioned in Section 6.6.
As in all blood coagulation preparations, the efficacy and tolerance of the medicinal product may be impaired by being mixed with other medicinal products. It is advisable to rinse a common venous access with a suitable solution, e.g. with isotonic saline solution, before and after the administration of FEIBA.

Coagulation factors derived from human plasma may be adsorbed by the inner surfaces of certain types of injection/infusion devices. If this were to occur, it could result in failure of therapy. Therefore, only approved plastic infusion devices may be used with FEIBA.

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 3 hours at room temperature (up to 25 °C). From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination (controlled and validated aseptic conditions), the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Reconstituted product must not be refrigerated.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.
Store in the original package in order to protect from light. For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The powder is supplied in a vial made of surface treated, colourless glass (hydrolytic type I for 500 U, and 2 500 U; hydrolytic type II for 1 000 U). The solvent is supplied in a vial made of surface treated, colourless glass (hydrolytic type I for 10 ml, 20 ml and 50 ml). The vials are closed by a stopper made of butyl rubber.

FEIBA 50 U/ml is available in the following presentations:

1 x 500 U
1 x 1 000 U
1 x 2 500 U

Presentation 500 U / 1 000 U contains either

- 1 vial with 500 U / 1 000 U FEIBA powder for solution for infusion
- 1 vial with 10 ml / 20 ml Water for Injections
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle
- 1 filter needle
- 1 transfer needle
- 1 aeration needle

or

- 1 vial with 500 U / 1 000 U FEIBA powder for solution for infusion
- 1 vial with 10 ml / 20 ml Water for Injections
- 1 BAXJECT II Hi-Flow
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle

Presentation 2 500 U contains

- 1 vial with 2 500 U FEIBA powder for solution for infusion
- 1 vial with 50 ml Water for Injections
- 1 BAXJECT II Hi-Flow
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle

Not all pack sizes and pack variants may be marketed.

6.6 Special precautions for disposal and other handling

FEIBA is to be reconstituted immediately prior to administration. The solution should be used immediately (as the preparation does not contain preservatives).

Swirl gently until all material is dissolved. Ensure that FEIBA is completely dissolved; otherwise, less FEIBA Units will pass through the device filter.

After reconstitution, the solution should be inspected for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or have deposits.

Open containers must not be re-used.

Do not use the product if its sterile barrier has been breached, its package damaged or if it shows signs of deterioration.

Use only the included Water for Injections and the included device set for reconstitution. If devices other than those enclosed are used, ensure the use of an adequate filter with a pore size of at least 149 µm.

Do not refrigerate after reconstitution.

After complete reconstitution of FEIBA, its injection or infusion should be commenced immediately and must be completed within three hours following reconstitution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution of the powder for preparing a solution for infusion with needles:

1. Warm the unopened solvent vial (Water for Injections) to room temperature or max. +37 °C if necessary.
2. Remove the protective caps from the powder vial and solvent vial (Fig. A) and disinfect the rubber stoppers of both vials.
3. Open the protective cap from one end of the enclosed transfer needle by twisting, remove it and insert the needle through the rubber stopper of the solvent vial (Fig. B and C).
4. Remove the protective cap from the other end of the transfer needle taking care not to touch the exposed end!
5. Invert the solvent vial and insert the free end of the transfer needle through the rubber stopper of the powder vial (Fig. D). The solvent will be drawn into the powder vial by vacuum.
6. Disconnect the two vials by removing the transfer needle from the powder vial (Fig. E). Gently swirl the powder vial to accelerate dissolution.
7. Upon complete reconstitution of the powder, insert the enclosed aeration needle (Fig. F) and any foam will collapse. Remove the aeration needle.

Infusion:

1. Open one end of the protective cap from the enclosed filter needle by twisting, remove it and fit the needle on to the sterile disposable syringe. Draw the solution into the syringe (Fig. G).

Disconnect the filter needle from the syringe and slowly administer the solution intravenously with the enclosed infusion set (or the enclosed disposable needle).

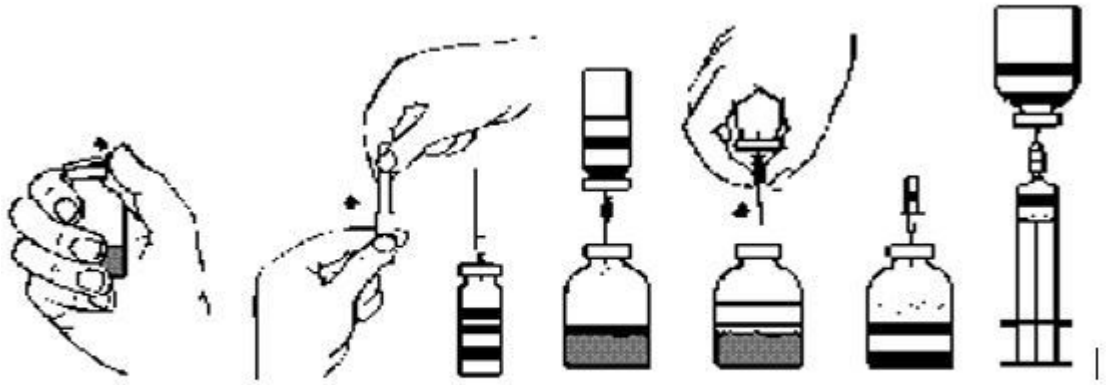
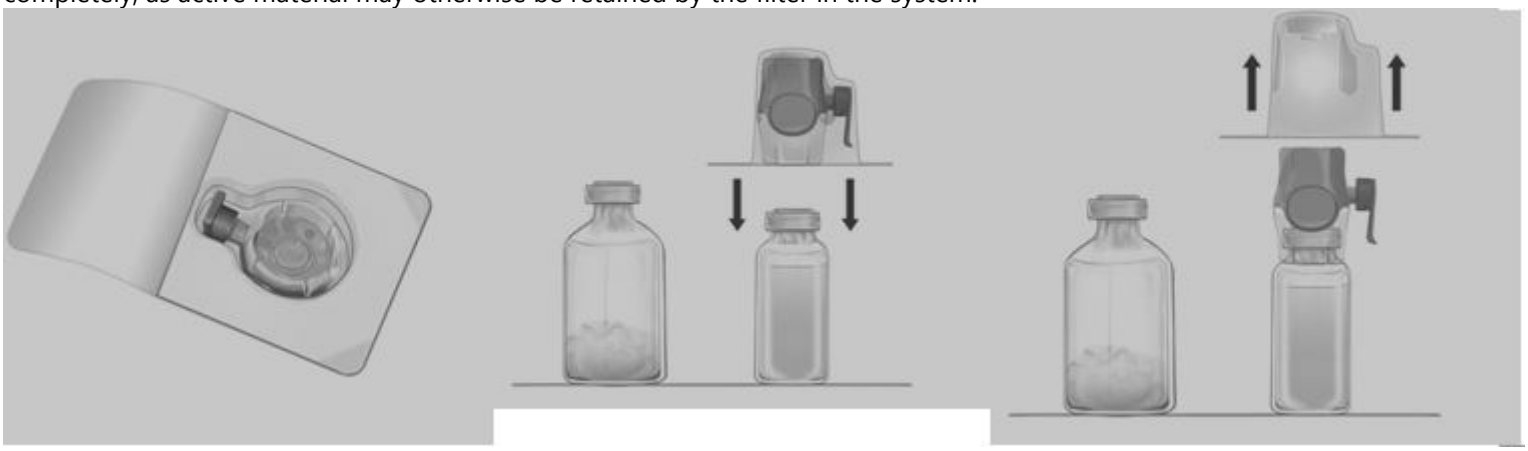


Fig. A Fig. B Fig. C Fig. D Fig. E Fig. F Fig. G

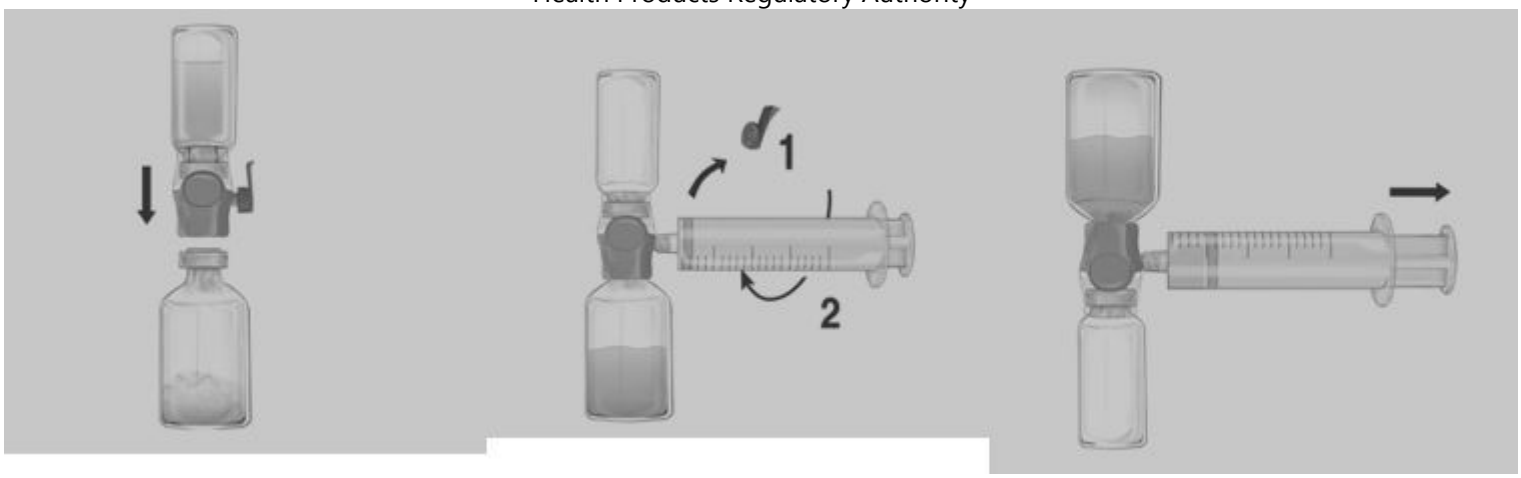
Reconstitution of the powder for preparing a solution for infusion with the BAXJECT II Hi-Flow:

1. Warm the unopened solvent vial (Water for Injections) to room temperature (15 °C to 25 °C), for example by using a water bath for several minutes (max. 37 °C) if necessary.
2. Remove the protective caps from the powder vial and solvent vial and disinfect the rubber stoppers of both vials. Place the vials on an even surface.
3. Open the packaging of the BaxJect ii Hi-Flow by pulling off the protective foil without touching the contents of the package (Fig. a). Do not remove the transfer system from the package at this point.
4. Turn the package around and press the transparent plastic pin through the rubber stopper of the solvent vial (Fig. b). Now remove the packaging from the BaxJect ii Hi-Flow (Fig. c). Do not remove the blue protective cap from the BaxJect ii Hi-Flow.
5. Now turn the system, consisting of the BaxJect ii Hi-Flow and the solvent vial, in such a way that the solvent vial is on top. Press the purple pin of the BaxJect ii Hi-Flow through the FEIBA vial. The solvent is drawn into the FEIBA vial by vacuum (Fig. d).
6. Swirl, but do not shake the entire system gently until the powder is dissolved. Make sure that the FEIBA has been dissolved completely, as active material may otherwise be retained by the filter in the system.



Infusion

1. Remove the blue protective cap from the BAXJECT II Hi-Flow. Tightly connect the syringe to the BAXJECT II Hi-Flow. DO NOT DRAW AIR INTO THE SYRINGE (Fig. e). In order to ensure tight connection between syringe and BAXJECT II Hi-Flow, the use of a luer lock syringe is highly recommended (turn syringe in clockwise direction until stop position when mounting).
2. Invert the system so that the dissolved product is on top. Draw the dissolved product into the syringe by pulling the plunger back SLOWLY and ensure that the tight connection between BAXJECT II Hi-Flow and the syringe is maintained throughout the whole pulling process (Fig. f).
3. Disconnect the syringe.
4. If foaming of the product in the syringe occurs, wait until the foam is collapsed. Slowly administer the solution intravenously with the enclosed infusion set (or disposable needle).



Donot exceed an infusion rate of 2 U FEIBA/kg body weight per minute.

7 MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

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