Docusign Envelope ID: 468F86FA-23E7-4CF1-B33B-C99D1B0B8B50

Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

FEIBA® 500 U

FEIBA® 1 000 U

(Powder and solvent for solution for injection)

Descriptive Name of Medicine:

Anti-Inhibitor-Coagulant Complex

Steam Treated

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Factor VIII Inhibitor Bypassing Activity

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FEIBA® 500 U:

1 ml contains 25 U* factor VIII inhibitor bypassing activity when reconstituted with 20 ml Water for Injections.

1 ml contains 50 U* factor VIII inhibitor bypassing activity when reconstituted with 10 ml Water for Injections.

1 ml contains 100 U* factor VIII inhibitor bypassing activity when reconstituted with 5 ml Water for Injections.

FEIBA is presented as powder and solvent to prepare a solution for infusion containing 200 – 600 mg human plasma protein with a Factor Eight Inhibitor Bypassing Activity of 500 U* per vial.

FEIBA® 1 000 U:

1 ml contains 50 U* factor VIII inhibitor bypassing activity when reconstituted with 20 ml Water for Injections.

1 ml contains 100 U* factor VIII inhibitor bypassing activity when reconstituted with 10 ml Water for Injections.

FEIBA is presented as powder and solvent to prepare a solution for infusion containing 400 – 1 200 mg human plasma protein with a Factor Eight Inhibitor Bypassing Activity of 1 000 U* per vial.

List of excipients: sodium chloride, sodium citrate dihydrate, sterilised water for injections.

For the full list of excipients, see section 6.1.

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FEIBA also contains factors II, IX and X mainly in non-activated form as well as activated factor VII. Factor VIII coagulant antigen (F VIII C: Ag) is present in a concentration of up to 0,1 U/1 U FEIBA. The preparation contains only traces of factors of the kallikrein-kinin system, if any at all. FEIBA is prepared from pooled human plasma.

All plasma units are exclusively obtained from licensed blood banks and licensed plasmapheresis centres in Europe and the United States of America. All blood donors are volunteers.

Each unit of plasma used for manufacture of FEIBA has been tested for HBs- antigen, HIV-1 antibody, HIV-2 antibody and HCV antibody and found negative by licensed assays.

To further reduce the potential risk of viral transmission, the product is steam treated under product-specific conditions (at 60 °C for 10 hours and at 80 °C for 1 hour) during production.

In HIV spiked samples of FEIBA this treatment inactivated at least 10^6 $TCID_{50}$/ml in 3 hours.

* 1 unit of FEIBA is defined as that amount of factor VIII inhibitor bypassing activity which shortens the activated partial thromboplastin time (APTT) of a high titre F VIII inhibitor plasma to 50 % of the buffer value (blank).

3 PHARMACEUTICAL FORM

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Powder and solvent for solution for injection.

White, off-white or pale green powder. The pH value of the ready-to-use solution is between 6,8 – 7,6 (for 25 U/mL and 50 U/mL), 6,5 – 7,3 (for 100 U/mL)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FEIBA is indicated for therapy and prophylaxis of haemorrhage and to cover surgical interventions in:

- Haemophilia A patients with F VIII inhibitor
- Haemophilia B patients with F IX inhibitor

FEIBA may be used in combination with Factor VIII concentrate for a continual long-term therapy to achieve an elimination of the factor VIII inhibitor or at least a reduction of the titre (BRACKMANN et al., 1981).

In addition, the successful use of FEIBA was described in a few non-haemophiliacs with acquired inhibitors to factors VIII, XI and XII as well as in a patient with von Willebrand's disease with an inhibitor.

4.2 Posology and method of administration

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Posology

Treatment should be initiated and supervised by a medical doctor experienced in the management of haemophilia.

Since a single dose of FEIBA contains considerably less F VIII coagulant antigen than Factor VIII concentrate, FEIBA is the treatment of choice in high responder patients, even if the current inhibitor titre is low.

As a general guideline a dose of 50 to 100 units of FEIBA per kg bodyweight is recommended, however, not exceeding a daily dose of 200 U/kg bodyweight unless the severity of bleeding warrants and justifies the use of higher doses. See section 4.4.

Dosage is independent of the patient's inhibitor titre. Since the response to treatment may differ from patient to patient the dosage recommendations are only guidelines.

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.

Dosage

Guidelines for Treatment of Patients with Inhibitors

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Inhibitor titre (BU*/ml)	Response to F VIII treatment	Minor to moderate Bleeding	Severe to life-threatening bleeding, surgery
< 5	low responder	F VIII or FEIBA	F VIII or FEIBA
5 – 10	high responder		FEIBA
	low responder	FEIBA	FEIBA
> 10	high responder	F VIII or FEIBA	FEIBA
	low responder		FEIBA
	high responder	FEIBA	FEIBA
		FEIBA	
		FEIBA	

*1 Bethesda Unit is defined as that amount of antibody that will inhibit 50 % of the F VIII activity of fresh average human plasma after incubation for 2 hours at 37 ℃.

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1. Spontaneous Bleeding

Joint, Muscle and Soft Tissue Haemorrhage

For minor to moderate bleedings a dose of 50 - 75 U/kg bodyweight is recommended at 12-hour intervals. Treatment should be continued until clear signs of clinical improvement appear, such as relief of pain, reduction of swelling or mobilisation of the joint.

For major muscle and soft tissue haemorrhage, such as retroperitoneal bleeding, doses of 100 U/kg bodyweight at 12-hour intervals are recommended.

Mucous Membrane Bleeding

A dose of 50 U/kg bodyweight is recommended to be given at 6-hour intervals under careful monitoring of the patient (visible bleeding site, repeated measurements of the patient's haematocrit). Again, if haemorrhage does not stop, the dose may be increased to 100 U/kg bodyweight taking care not to exceed the maximum daily dose of 200 U/kg bodyweight.

Other Severe Haemorrhages

Severe haemorrhages, such as CNS bleedings have been effectively treated with doses of 100 U/kg bodyweight at 12-hour intervals. In individual cases FEIBA may be given at intervals of 6 hours until clear clinical improvement is achieved. (Do not exceed the maximum daily dose).

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!)

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3. Prophylaxis in haemophilia A patients with inhibitors

Prophylaxis of bleeding in patients with a high inhibitor titer 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 titer 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 titer has decreased to < 2 B.U.*

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 medicine, it is recommended that a platelet count be performed because a sufficient number of functionally intact platelets is considered to be necessary for the efficacy of the medicine.

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Coagulation tests such as the whole blood clotting time (WBCT), the thrombelastogramme (TEG, r-value), and the aPTT usually show only a minor shortening and need not correlate with clinical improvement. For this reason, these tests can only be used for monitoring of FEIBA therapy to a very limited extent.

Due to the complex mechanism of action, no direct monitoring of active ingredients is available.

Method of administration

FEIBA : 500 U / 20 ml & 500 U / 10 ml

FEIBA: 1000 U / 20 ml

FEIBA must be administered as an intravenous injection or infusion. The rate of administration should ensure the comfort of the patient and should not exceed a maximum of 2 U / kg body weight per minute.

FEIBA: 500 U / 5 ml & 1000 U / 10ml

FEIBA should be infused at an infusion rate of 2 U/kg body weight per minute. In patients who have tolerated the infusion rate of 2 U / kg body weight per minute well, in subsequent infusions the rate may be increased up to a maximum of 10 U / kg body weight per minute. See section 5.1.

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

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4.3 Contraindications

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

- Hypersensitivity to the medicine
- Disseminated intravascular coagulation (DIC)
- Acute thrombosis or embolism (including myocardial infarction)

4.4 Special warnings and precautions for use

Allergic-Type 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.

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

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.

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When considering re-exposure to FEIBA in patients with known or suspected hypersensitivity to the medicine, 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 nonallergic), including potential remedial and/or preventative therapy or alternative therapeutic medicines. (See section 4.8).

Thromboembolic Events

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 may increase 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 in patients at risk of DIC, arterial or venous thrombosis. (See contraindications).

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 medical doctor (see also section 4.5).

At the first signs or symptoms of thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

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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 medicine should be given only for as long as absolutely necessary to achieve the therapeutic goal.

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 titer 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 ischemia, 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.

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Monitoring of Therapy

Single doses of 100 units per kg bodyweight of FEIBA and daily doses of 200 units per kg bodyweight of FEIBA should not be exceeded. Patients given single doses of 100 units FEIBA per kg bodyweight or more should be monitored for the development of Disseminated Intravascular Coagulation and/or symptoms of acute coronary ischaemia and for symptoms of other thrombotic or thromboembolic events.

High doses of FEIBA should be given only as long as absolutely necessary to stop bleeding.

In case of changes in blood pressure, pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly and appropriate diagnostic and therapeutic measures are to be initiated.

Laboratory indications of Disseminated Intravascular Coagulation are decreased fibrinogen, decreased platelet count, and/or presence of fibrin/fibrinogen degradation products (FDP). Other indications of Disseminated Intravascular Coagulation include significantly 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 non haemophilic patients with acquired inhibitors against factors VIII, IX or XII may have both a bleeding tendency and an increased risk of thrombosis at the same time.

Measures to prevent transmission of infectious medicines

Standard measures to prevent infections resulting from the use of medicines 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 medicines prepared from human blood or plasma are administered, the possibility of transmitting infective medicines cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

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The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for the nonenveloped virus HAV. The measures taken may be of limited value against nonenveloped 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 (against hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma-derived products including FEIBA.

Discordant Response to Bypassing Medicines

Due to patient-specific factors the response to a bypassing medicine can vary, and in a given bleeding situation patients experiencing insufficient response to one medicine may respond to another medicine. In case of insufficient response to one bypassing medicine, use of another medicine 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.

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.

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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).

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.

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 (see section 5.1, literature case reports, n = 46, and clinical data in prophylaxis study 090701, n = 1, and PASS-EU-006, n = 1)

Elderly

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

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Paediatric population

Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age.

Excipient related considerations

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

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

The recording of the medicine name and batch number is strongly recommended following each administration of this medicine in order to be able to identify the batch of medicine received.

4.5 Interaction with other medicinal products and other forms of interaction

As for any blood coagulation factor concentrate, FEIBA should not be mixed with other medicines before administration as this might impair the efficacy and safety of the product. It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of FEIBA.

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

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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 and FEIBA should be administered at least 6 to 12 hours apart.

In cases of concomitant rFVIIa use, according to available in vitro data and clinical observations a potential medicine interaction may occur (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

The safety of FEIBA for use in pregnant or breastfeeding women has not been established.

Pregnancy

There are no adequate data from the use of FEIBA in pregnant women. The pregnancy confers an increased risk of thrombosis, and several complications of pregnancy that are associated with an increased risk of DIC.

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Breastfeeding

There are no adequate data from the use of FEIBA in breastfeeding 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, medical doctors should balance the potential risks and only prescribe FEIBA if clearly needed, taking into consideration that pregnancy and the postpartum period confer 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

No effects on the ability to drive and use machines have been observed.

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 section 4.4).

The adverse reactions presented in this section have been reported from post marketing surveillance as well as 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

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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

System Organ Class (SOC)	Preferred current MedDRA Term	Frequency Category*
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Increase of inhibitor titer (anamnestic response) [a]	Unknown
	Disseminated intravascular coagulation (DIC)[d]	Unknown
IMMUNE SYSTEM DISORDERS	Hypersensitivity[c]	Common
	Urticaria	Unknown
	Anaphylactic reaction[d]	Unknown
NERVOUS SYSTEM DISORDERS	Somnolence	Unknown
	Dizziness[b]	Common
	Dysgeusia	Unknown
	Headache[c]	Common
	Paresthesia[d]	Unknown
	Hypaesthesia	Unknown
	Thrombotic stroke[d]	Unknown

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	Embolic stroke[d]	Unknown
Cardiac disorders	Cardiac infarction[d]	Unknown
	Tachycardia[d]	Unknown
VASCULAR DISORDERS	Hypotension	Common
	Thrombosis[d]	Unknown
	Venous thrombosis[d]	Unknown
	Arterial thrombosis[d]	Unknown
	Embolism (thromboembolic complications)	Unknown
	Hypertension[d]	Unknown
	Flushing[d]	Unknown
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Dyspnea	Unknown
	Pulmonary embolism[d]	Unknown
	Bronchospasm[d]	Unknown
	Wheezing[d]	Unknown
	Cough[d]	Unknown
GASTROINTESTINAL DISORDERS	Nausea	Unknown
	Vomiting[d]	Unknown
	Diarrhea[d]	Unknown
	Abdominal discomfort[b]	Unknown
SKIN AND SUBCUTANEOUS	Rash[c]	Common
	Sensation of numbness in the face	Unknown

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	Angioedema[d]	Unknown
	Urticaria[d]	Unknown
	Pruritus[d]	Unknown
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills	Unknown
	Pyrexia	Unknown
	Chest pain	Unknown
	Chest discomfort	Unknown
	Pain at the injection site[d]	Unknown
	Malaise[d]	Unknown
	Feeling hot[d]	Unknown
INVESTIGATIONS	Hepatitis B surface antibody positive[c]	Common
	Drop in blood pressure	Unknown
	Fibrin D-dimer increased	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.

[d]The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC)

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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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

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 have occurred with doses above 200 U/kg or with patients with other risk factors for thromboembolic events.

If signs or symptoms of thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated (See section 4.4)

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Class: A 30,3 Blood Fractions

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 (F II) and activated factor X (FXa) in the mode of action of FEIBA.

Mechanism of action

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.

Pharmacodynamic effects

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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 7324 U. In addition, 48 patients in literature are available 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).

Clinical efficacy and safety

The tolerability and safety of FEIBA, reconstituted in regular or 50 % reduced volume and of faster infusion rates in haemophilia patients with inhibitors was investigated in a prospective, open-labeled, and randomized crossover study (091501). Thirty-three patients were treated, and twenty-eight patients completed the study. In the study, FEIBA was reconstituted in 50 % reduced volume (100 U/ml concentration) and infused IV at infusion rates of 2, 4 and 10 /kg/min at the

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labelled dose of 85 U/kg ± 15 U/kg for all patients. The primary endpoints were tolerability and safety with the 50 % reduced volume (increased concentration) at standard and increased infusion rates. The study demonstrated that both the higher concentration (100 U/ml) and the higher infusion rates (4 and 10 U/kg/min) were well tolerated and that the safety profile was comparable at the labelled dose of 85 U/kg ± 15 U/kg. The patients who received the 50 % reduced volume (increased concentration) at the standard infusion rate of 2 U/kg/min had similar rates of related treatment emergent adverse events (TEAEs) compared to those who received the regular volume (50 U/ml concentration) with the same infusion rate. No related TEAEs were reported at the infusion rate of 4 U/kg/min. Patients who received the 50 % reduced volume (100 U/ml) at the infusion rate of 10 U/kg/min experienced 1 related, non-serious TEAE In addition, the patients who received the 50 % reduced volume (increased concentration) at the increased infusion rates of 4 and 10 U/kg/min did not experience any serious TEAE, any hypersensitivity reaction, any infusion site reaction, any thrombotic TEAE, or any TEAE leading to drug withdrawal or study discontinuation. Overall, the TEAEs seen in the study were consistent with the known safety profile of FEIBA in patients with haemophilia with inhibitors.

In an open, uncontrolled, non-interventional observational post-authorization safety study of FEIBA (PASS-EU-006), 75 patients (mean age 34,8 years, 70 males and 5 females), of which 73 had haemophilia A with inhibitors and 2 haemophilia B with inhibitors, were treated with FEIBA. Of the 65 patients with congenital haemophilia, 63 had congenital haemophilia A and 2 had congenital haemophilia B. At baseline, 43 patients were prescribed FEIBA for prophylaxis and 32 were prescribed FEIBA for on-demand treatment. Higher infusion rates (> 2 U/kg/min) were used in 6 paediatric patients with age between 11 months and 11 years and in 5 adolescents with age 13 to 16 years.

Paediatric population

Out of 320 infusions with an available infusion rate in 7 paediatric and 6 adolescent patients, there were 129 infusions (40,3 %) in 2 patients (both paediatric) with infusion rate > 10 U/kg/min, 26 infusions (8,1 %) in 7 patients (4 paediatric; 3 adolescents) with infusion rate > 4 and ≤ 10 U/kg/min, 135 infusions (42,2 %) in 7 patients (3 paediatric; 4 adolescents) with infusion rate > 2 and ≤ 4 U/kg/min, and 30 infusions (9,4 %) in 3 patients (1 paediatric; 2 adolescents) with infusion rate ≤ 2 U/kg/min.

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.

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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.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium citrate

Water for Injections

6.2 Incompatibilities

No compatibility studies have been performed with the medicine. Therefore, FEIBA must not be mixed with other medicines or solvents.

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.

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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

Store at or below 25 °C. Do not freeze. Discard if frozen.

FEIBA must not be used beyond the expiry date indicated.

Store in the original package in order to protect from light. For storage conditions of the reconstituted medicinal product – see section 6.3.

6.5 Nature and contents of container

The powder is supplied in a vial made of surface treated, colorless glass (hydrolytic type I for 500 U/ 5ml and 500 U/ 10ml).

The powder is supplied in a vial made of surface treated, colorless glass (hydrolytic type II for 1 000 U).

The solvent is supplied in a vial made of surface treated, colorless glass (hydrolytic type I).

The vials are closed by a stopper made of butyl rubber.

Kit for reconstitution and injection.

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The reconstituted solution is colourless to slightly yellowish and clear to slightly turbid. It is essentially free from visible particles.

PACKS

FEIBA 500 U + 5 ml Solvent

- R/C vial containing 500 FEIBA-units, lyophilized
- R/C vial containing 5 ml water for injections
- Kit for reconstitution and injection*

FEIBA 500 U + 10 ml Solvent

- R/C vial containing 500 FEIBA-units, lyophilized
- R/C vial containing 10 ml water for injections
- Kit for reconstitution and injection*

FEIBA 500 U + 20 ml Solvent

- R/C vial containing 500 FEIBA-units, lyophilized
- R/C vial containing 20 ml water for injections
- Kit for reconstitution and injection*

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FEIBA 1 000 U + 10 ml Solvent

- R/C vial containing 1 000 FEIBA-units, lyophilized
- R/C vial containing 10 ml water for injections
- Kit for reconstitution and injection*

FEIBA 1 000 U + 20 ml Solvent

- R/C vial containing 1 000 FEIBA-units, lyophilized
- R/C vial containing 20 ml water for injections
- Kit for reconstitution and injection*

*Kit for reconstitution and injection:

Transfer needles:

- Transfer needle (stainless steel, gamma-irradiated)
- Filter needle (stainless steel, gamme-irradiated)
- Disposable needle (hub and needle shield: PP, canula: stainless steel, ETO sterilized-residual ETO content: < 1 ppm)
- Butterfly needle (needle: stainless steel; tube: PVC; cap:PE; ETO sterilized-residual ETO content: < 1 ppm)
- Aeration needle (stainless steel, ETO sterilized-residual ETO content: < 1 ppm)
- Disposable syringe (PP, ETO sterilized-residual ETO content: < 1 ppm)

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or

Baxject II Hi-Flow:

- 1 BAXJECT II Hi-Flow for reconstitution
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

- FEIBA is to be stored in lyophilized condition and should only be reconstituted immediately before application.
- The solution should be used immediately (as the preparation does not contain preservatives).
- Aseptic technique should be used throughout the reconstitution process.
- The solution must then be used as promptly as practicable, however, within a maximum of 3 hours.
- 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.

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- Open containers must not be re-used.
- Do not use the medicine if its sterile barrier has been breached, its package damaged or if it shows signs of deterioration.
- FEIBA may be reconstituted with either Transfer Needles or with the Baxject II Hi-Flow device.
- 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.

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

Reconstitution of Concentrate for FEIBA : 500 U / 20 ml , 500 U / 10 ml , 1000 U / 20 ml

Transfer Needles

1. Warm the unopened bottles containing the solvent to room temperature (max. 37 °C).
2. Remove the caps from the concentrate and solvent bottles (fig. A) and disinfect the rubber stoppers of both bottles.
3. The enclosed transfer needle (double-ended needle) is protected by 2 plastic caps sealed by a weld mark. Break the weld (fig. B) by twisting and remove one cap. Insert the exposed needle into the rubber stopper of the solvent bottle (fig. C).
4. Remove the other cap from the double-ended needle taking care not to touch the exposed end.
5. Invert the solvent bottle over the concentrate bottle, and insert the free end of the double-ended needle to approximately half the needle length into the rubber stopper of the concentrate bottle (fig. D). The solvent will be drawn into the concentrate bottle which is under vacuum.

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6. Disconnect the two bottles by removing the needle from the concentrate bottle (fig. E). Gently agitate or rotate the concentrate bottle to accelerate dissolution.

7. Upon complete reconstitution of the concentrate insert the enclosed aeration needle (fig. F) and any foam will collapse. Remove the aeration needle.

Instructions for Injection/Infusion:

Remove the protective covering from the enclosed filter needle by turning the cap and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. G).

Disconnect the filter needle from the syringe and slowly inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

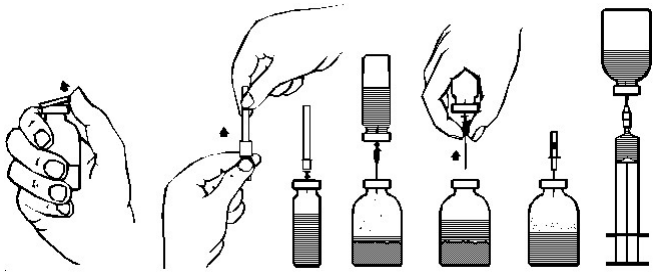


Fig.A Fig.B Fig.C Fig.D Fig.E Fig.F Fig.G

Baxject II Hi-Flow

1. Warm the unopened vial containing the solvent (sterilised water for injections) to room temperature, e.g. using a sterile water bath for warming within

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several minutes (max. +37 °C) if necessary.

2. Remove the protective caps from the FEIBA vial and solvent vial and cleanse the rubber stoppers of both. Place the vials on a flat surface.

3. Open the package of BAXJECT II Hi-Flow device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the transfer device from the package.

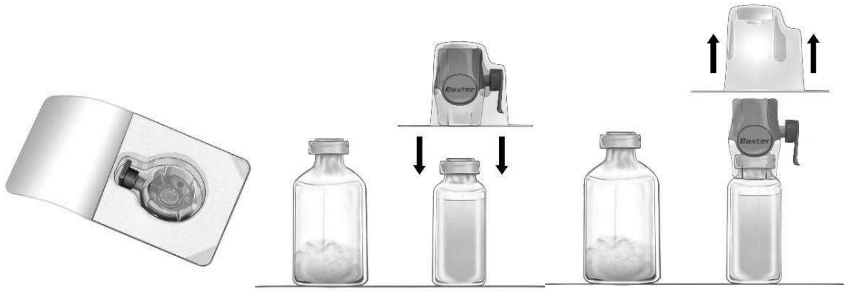
4. Turn the package over and insert the clear plastic spike through the solvent stopper (Fig. b). Grip the package at its edge and pull the package off BAXJECT II Hi-Flow (Fig. c). Do not remove the blue cap from BAXJECT II Hi-Flow.

5. With the transfer device attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the purple plastic spike of BAXJECT II Hi-Flow through the FEIBA vial stopper. The vacuum will draw the solvent into the FEIBA vial (Fig. d).

6. Swirl, but do not shake, the entire system gently until all material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

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Fig. a Fig. b Fig. c



Instructions for Injection/Infusion:

1. Remove the blue cap from BAXJECT II Hi-Flow. Tightly connect the syringe to 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 FEIBA solution 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 a disposable needle).

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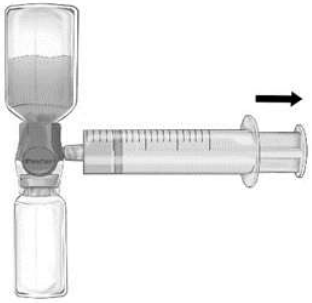
Fig. d



Fig. e



Fig. f



Do not exceed an injection/infusion rate of 2 units FEIBA per kg of bodyweight per minute.

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Reconstitution of Concentrate for FEIBA: 500 U / 5 ml & 1000 U / 10ml

Baxject II Hi-Flow

1. Warm the unopened vial containing the solvent (sterilised water for injections) to room temperature, e.g. using a sterile water bath for warming within several minutes (max. +37 °C) if necessary.

2. Remove the protective caps from the FEIBA vial and solvent vial and cleanse the rubber stoppers of both. Place the vials on a flat surface.

3. Open the package of BAXJECT II Hi-Flow device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the transfer device from the package.

4. Turn the package over and insert the clear plastic spike through the solvent stopper (Fig. b). Grip the package at its edge and pull the package off BAXJECT II Hi-Flow (Fig. c). Do not remove the blue cap from BAXJECT II Hi-Flow.

5. With the transfer device attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the purple plastic spike of BAXJECT II Hi-Flow through the FEIBA vial stopper. The vacuum will draw the solvent into the FEIBA vial (Fig. d).

6. Swirl, but do not shake, the entire system gently until all material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

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Fig. a Fig. b Fig. c



Instructions for Injection/Infusion:

1. Remove the blue cap from BAXJECT II Hi-Flow. Tightly connect the syringe to 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 FEIBA solution 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 a disposable needle).

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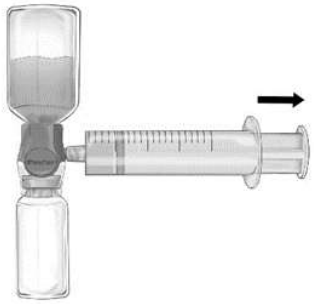
Fig. d



Fig. e



Fig. f



Do not exceed an infusion rate of 10 U FEIBA/kg body weight per minute.

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7 HOLDER OF THE CERTIFICATE OF REGISTRATION:

Takeda (Pty) Ltd

Building A, Monte Circle

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Fourways 2191

Gauteng, South Africa

8 REGISTRATION NUMBER(S)

FEIBA 500 U: T/30.3/597

FEIBA 1 000 U: T/30.3/598

9 DATE OF AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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