F E I B A

Factor VIII Inhibitor
Bypassing Activity

International Summary of Product Characteristics

Please consult your country-specific Summary of Product Characteristics before using the product as licenses and licensing conditions may vary from country to country.
1. NAME OF THE MEDICINAL PRODUCT

FEIBA 500 U / 1000 U, powder and solvent for solution for injection
Factor VIII Inhibitor Bypassing Activity

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FEIBA is presented as powder and solvent to prepare a solution for injection containing 200-600 mg (400-1200 mg) human plasma protein with a Factor Eight Inhibitor Bypassing Activity of 500 U* (1000 U) per vial.
The final solution has an activity of approximately 25 U/ml (500 U pack size) or 50 U/ml (1000 U pack size) when reconstituted with 20 ml of Sterilised Water for Injections.

FEIBA 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 factors of the kallikrein-kinin system are present only in trace amounts, if at all.

*) A solution containing 1 U of FEIBA shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma to 50% of the buffer value (blank).

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.
The product is presented as freeze-dried powder or friable solid of white to off-white or pale green colour.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

6. Treatment and prophylaxis of bleeding in haemophilia A patients with Factor VIII inhibitor
7. Treatment and prophylaxis of bleeding in haemophilia B patients with Factor IX inhibitor
8. Treatment and prophylaxis of bleeding in non haemophiliacs with acquired inhibitors to Factors VIII, IX, XI.

FEIBA is also used in combination with Factor VIII concentrate for long-term therapy to avoid breakthrough bleeding during ITI.
In three cases FEIBA was also used in patients with an inhibitor to von-Willebrand Factor.

4.2. Posology and Method of Administration

Treatment should be initiated and supervised by a physician experienced in the management of haemophilia.
**Posology**

The dosage and duration of the therapy is dependent upon the severity of the disorder, the location and extent of the bleeding and the patient’s clinical condition.

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

As a general guide, a dose of 50 to 100 U of FEIBA per kg bodyweight (bw) is recommended, however, a single dose of 100 U/kg bw and a daily dose of 200 U/kg bw should not be exceeded.

**Monitoring**

Coagulation tests such as whole blood clotting time (WBCT), the thromboelastogram (TEG, r-value), and the aPTT usually show only a minor shortening and may not correlate with clinical improvement. Consequently, these tests are only of very limited value in monitoring FEIBA therapy.

1. **Spontaneous Haemorrhage**

   **Joint, Muscle and Soft Tissue Haemorrhage**

   For minor to moderate bleeding a dose of 50-75 U/kg bw 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, a dose of 100 U/kg bw at 12-hour intervals is recommended.

   **Mucous Membrane Haemorrhage**

   A dose of 50 U/kg bw is recommended every 6 hours with careful monitoring of the patient (visible bleeding site, repeated measurements of haematocrit). If the haemorrhage does not stop, the dose may be increased to 100 U/kg bw. (A maximum daily dose of 200 U/kg bw should not be exceeded.)

   **Other Severe Haemorrhages**

   Severe haemorrhages, such as CNS bleeding, have been effectively treated with doses of 100 U/kg bw at 12-hour intervals. In individual cases FEIBA may be given at 6-hour intervals until clear clinical improvement is achieved. (A maximum daily dose of 200 U/kg bw should not be exceeded.)

2. **Surgery**

   50-100 U/kg bw should be given at intervals of up to 6 hours, a maximum daily dose of 200 U/kg bw should not be exceeded.

3. **Prophylaxis**

   Bleeding prophylaxis in haemophilia A patients with inhibitors has been performed during immune tolerance therapy (ITI), or after ITI failure.
In patients with high responding inhibitors and a history of frequent bleeding, FEIBA may be given concomitantly with factor VIII concentrate in a dose range of 50 to 100 U/kg bw twice a day until the reduction of the factor VIII inhibitor to 1 B.U.*.

If immune tolerance with high-dose factor VIII therapy cannot be induced, a monotherapy of 50 to 100 U/kg bw three times a week may be indicated for bleeding prophylaxis.

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

**Method of Administration**

Reconstitute the product for administration as described in section 6.6. Inject the solution slowly. The rate of administration should ensure the comfort of the patient, not exceeding a maximum of 2 U/kg bw per minute.

**4.3. Contraindications**

Depending on therapeutic alternatives, the contraindications below are to be considered relative or absolute.

- Hypersensitivity to the active substance or to any of the excipients.

In the following situations FEIBA should only be used if - for example due to a very high inhibitor titre - no response to treatment with the appropriate coagulation factor concentrate can be expected.

- Disseminated Intravascular Coagulation (DIC):
  
  Laboratory and/or clinical symptoms that are clearly indicative of liver damage: due to the delayed clearance of activated coagulation factors such patients are at an increased risk of developing DIC.

- Myocardial Infarction, Acute Thrombosis and/or Embolism
  
  In patients with a tentative or definite diagnosis of coronary heart disease as well as in patients with acute thrombosis and/or embolism, the use of FEIBA should only be used in life-threatening bleeding episodes.

**4.4. Special Warnings and Special Precautions for Use**

As with any intravenous protein product, allergic-type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, pruritus, generalised urticaria, tightness of the chest, wheezing and hypotension.

If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.
In case of anaphylactic shock, the current medical standards for shock treatment should be observed.

As the quantity of sodium in the maximum daily dose may exceed 200 mg, it should be accounted for in patients on a low sodium diet.

Single doses of 100 U/kg bw and daily doses of 200 U/kg bw should not be exceeded. Patients given single doses of 100 U/kg bw should be monitored for the development of DIC or symptoms of acute coronary ischaemia. High doses of FEIBA should be given only for as long as absolutely necessary to stop the bleeding.

Where there are significant clinical changes in blood pressure, pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated. Laboratory results indicative of DIC are decreased fibrinogen values, decreased platelet count, and/or presence of fibrin/fibrinogen degradation products (FDP).

There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, inhibitor formation is a common occurrence in haemophilic children undergoing factor VIII replacement therapy. Case studies have shown the successful use of FEIBA in the young age group.

**Acquired inhibitors**
Non-haemophilic patients with acquired inhibitors to coagulation factors may have a concurrent bleeding tendency and increased risk of thrombosis.

**Laboratory Tests and Clinical Efficacy**
In vitro tests to control efficacy such as aPTT, whole blood clotting time (WBCT), and thromboelastogram (TEG) may not correlate with clinical improvement. For this reason, attempts to normalise these values by increasing the dose of FEIBA may not be successful and are strongly discouraged because of the potential hazard of inducing DIC by overdosage.

**Significance of Platelet Count**
In case of inadequate response to FEIBA treatment it is recommended that a platelet count be performed, since a sufficient number of functionally intact platelets is considered to be necessary for the efficacy of FEIBA.

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 totally be 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 red cell turnover (e.g. in haemolytic anaemia).
Appropriate vaccination should be considered for patients in regular/repeated receipt of plasma derived coagulation factor concentrates. Vaccination against hepatitis A and B is recommended. The recording of the product name and batch number is strongly recommended following each administration.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

It is not recommended to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA.

If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA is indicated, the products should be administered at least 6 hours apart.

4.6. Pregnancy and Lactation

Animal reproduction studies have not been conducted with FEIBA based on the rare occurrence of haemophilia in women. Experience regarding the use of FEIBA during pregnancy and breast feeding is not available. Therefore, due to the increased risk of thrombosis during pregnancy, FEIBA should only be used under careful medical monitoring and if no alternative therapy is available.

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

No related adverse events were reported from clinical trials. The undesirable effects reported in the listing hereafter are based on post-market experience for FEIBA. Their frequency has been evaluated by using the following criteria: very common (≥ 1/10), common (< 1/10 to ≥ 1/100), uncommon (< 1/100 to ≥ 1/1,000), rare (< 1/1,000 to ≥ 1/10,000) and very rare (<1/10,000).

The undesirable effects listed below reflect the type of undesirable effects that may be reported with FEIBA. Their incidence rate is <1/10 000, i.e. very rare.

**Blood and lymphatic system disorders**
- Disseminated intravascular coagulation

**Cardiac disorders**
- Myocardial infarction

**General disorders and administration site conditions**
- Stabbing pain
Immune system disorders
- Anaphylaxis, hypersensitivity reactions (including allergic reactions), urticaria

Nervous system disorders
- Numbness in the face and extremities (hypoesthesia)

Vascular disorders
- Drop in blood pressure (hypotension), thromboembolic complications

Rapid intravenous injection or infusion may cause a stabbing pain and numbness in the face and extremities as well as a drop in blood pressure.

Myocardial infarction was found to occur after doses exceeding the recommended maximum daily dose and/or prolonged administration and/or in the presence of risk factors predisposing to thromboembolic disease.

For safety with respect to transmissible agents, see 4.4

4.9. Overdose

Overdosage of FEIBA may increase the risk of undesirable effects such as thromboembolism, DIC or myocardial infarction (see section 4.4, Special Warnings and Special Precautions for Use).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: activated prothrombin complex against factor VIII antibodies, ATC Code: B02B D03

Although FEIBA was developed in the early 1970s and its factor VIII inhibitor bypassing activity has been demonstrated both in vitro and in vivo, its active principle is still the subject of scientific debate. However, recent scientific work indicates a role of specific components of the activated prothrombin complex, zymogen prothrombin (F II) and activated Factor X (FXa), in the FEIBA mode of action.

5.2. Pharmacokinetic Properties

Since FEIBA is composed of different coagulation factors with varying half-lives for the single components, it is not possible to make any definite statement with regard to the pharmacokinetic properties of FEIBA.
5.3. Preclinical Safety Data

Based on acute toxicity studies in factor VIII knockout mice and in normal mice and rats with doses exceeding the maximum daily dose in humans (i.e. >200 U/kg bw), it can be concluded that adverse effects related to FEIBA are primarily the result of hypercoagulation induced by the pharmacological properties of the product.

Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.

Since human plasma proteins are not seen to cause tumourigenic or mutagenic effects, experimental studies particularly in heterologous species are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Powder
- Sodium Chloride
- Sodium Citrate

Solvent
- Sterilised Water for Injection

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products or solvents. Only the provided infusion sets should be used.

6.3. Shelf Life

Two years. Stability studies support the stability of the reconstituted product for up to 3 hours at 20°C – 25°C. Nevertheless from a microbiological viewpoint, the product should be used immediately following reconstitution. Reconstituted product must not be returned to the refrigerator.

6.4. Special Precautions for Storage

Store at 2°C - 8°C. Do not freeze. Store in the original package to protect from light.

< country specific: Within the indicated shelf life the product may be stored at room temperature (up to +25°C) for single period not exceeding 6 months. Record the period of storage at room temperature below the expiry date indicated on the product package. At the end of this period, the product should be used or discarded.

Keep out of the reach and sight of children.
6.5. Nature and Contents of Container

FEIBA is supplied in vials with nominal potencies of 500 U and 1000 U Factor Eight Inhibitor Bypassing Activity, to be dissolved in 20 ml of Sterilised Water for Injection. Both powder and solvent come in vials of surface-treated soda lime glass of hydrolytic type II, closed with butyl rubber stoppers.
Each pack also contains: 1 BAXJECT (for needleless reconstitution) or alternatively 1 filter needle and 1 transfer needle and 1 aeration needle, 1 disposable syringe, 1 disposable needle, 1 winged butterfly needle.

6.6. Instructions for Use, Handling and Disposal

FEIBA should be reconstituted just prior to administration. The solution should then be used immediately as the preparation contains no preservatives. Do not use solutions that are cloudy or have deposits. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.

VARIANT A (WHEN BAXJECT IS SUPPLIED WITH THE PRODUCT):

Reconstitution of powder: use aseptic technique as described below

1. Warm the unopened vial containing the solvent (sterilised water for injection) to room temperature.
2. Remove the protective caps from the FEIBA and sterilised water (solvent) vials and cleanse the rubber stoppers of both.
3. Open the BAXJECT package by peeling away the lid without touching the inside (Fig. a).
4. Do not remove the device from the package. Turn the package over and fully insert the plastic spike through the centre of the solvent vial stopper. Lift the packaging away from the BAXJECT device (Fig. b).
5. Quickly turn over the solvent vial and BAXJECT so that the solvent vial is on top of the device and insert the exposed plastic spike through the stopper of the FEIBA vial. Solvent will be drawn into the powder vial by vacuum (Fig. c).
6. Swirl gently until all material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

Injection/Infusion:

1. Turn the tap on the BAXJECT device down (towards FEIBA powder vial) and remove the attached cap (Fig. d).
2. Before attaching the syringe, draw air into it by pulling back the plunger. Connect the syringe to the BAXJECT device, and inject the air into the FEIBA vial (Fig. e).

3. While keeping the syringe plunger in place, invert the system so that the FEIBA vial is on top. Draw the concentrate into the syringe by pulling the plunger back slowly (Fig. f).

4. Turn the BAXJECT tap back to its original sideways position and disconnect the syringe. **Do not exceed an injection/infusion rate of 2 units FEIBA per kg of body weight per minute.**

![Fig. a](image1.png) ![Fig. b](image2.png) ![Fig. c](image3.png)

![Fig. d](image4.png) ![Fig. e](image5.png) ![Fig. f](image6.png)

**VARIANT B (WHEN PRODUCT IS SUPPLIED WITH FILTER NEEDLE, TRANSFER NEEDLE AND AERATION NEEDLE FOR RECONSTITUTION INSTEAD OF BAXJECT):**

Reconstitution of powder: use aseptic technique as described below

1. Warm the unopened vial containing the solvent (sterilised water for injections) to room temperature.
2. Remove the protective caps from the FEIBA and solvent vials (fig. 1) and cleanse the rubber stoppers of both.
3. Remove the protective covering from one end of the supplied transfer needle by twisting and pulling (fig. 2). Insert the exposed needle through the rubber stopper of the solvent vial (fig. 3).
4. Remove the protective covering from the other end of the transfer needle taking care not to touch the exposed end.
5. Invert the solvent vial over the FEIBA vial, and insert the free end of the transfer needle through the rubber stopper of the vial (fig. 4). The solvent will be drawn into the powder vial by vacuum.

6. Disconnect the two vials by removing the needle from the FEIBA vial (fig. 5). Gently swirl the FEIBA vial to dissolve the powder.

7. Upon complete reconstitution insert the enclosed aeration needle provided (fig. 6) and any foam will collapse. Remove aeration needle.

**Injection/Infusion:**

1. Remove the protective covering from the supplied filter needle by twisting and pulling and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. 7).

2. Disconnect the filter needle from the syringe and slowly inject the solution intravenously with the enclosed winged set for injection (or the enclosed disposable needle).

If devices other than those supplied with FEIBA are used, ensure use of an adequate filter.

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

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

7. **MARKETING AUTHORISATION HOLDER**
   <country specific>

8. **MARKETING AUTHORISATION NUMBER(S)**
   <country specific>

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
   <country specific>

10. **DATE OF REVISION OF THE TEXT**
    <country specific>