EN

0756709

FEIBA 500 U, 1000 U

Factor VIII Inhibitor Bypassing Activity

QUALITATIVE AND QUANTITATIVE COMPOSITION

FEIBA	500 U*	1000 U*
Active Ingredient: Human Plasma Protein with a Factor Eight Inhibitor Bypassing Activity of	200-600 mg 500 units	400-1200 mg 1000 units
Other Ingredients: Sodium Chloride Sodium Citrate	 160 mg 80 mg	 160 mg 80 mg

*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).

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/1U FEIBA. The factors of the kallikrein-kinin system are present only in trace amounts, if at all.

PHARMACEUTICAL FORM AND CONTENTS

The product is supplied as a freeze-dried substance accompanied by the solvent.
FEIBA is available in sizes of 500 U and 1000 U, to be dissolved in 20 ml of sterilised water for injections. Each pack also includes a kit for reconstitution and injection.
The reconstituted product is intended for intravenous administration.

THERAPEUTIC INDICATIONS

- Treatment and prophylaxis of bleeding in haemophilia A patients with F VIII inhibitor
- Treatment and prophylaxis of bleeding in haemophilia B patients with F IX inhibitor
- Treatment and prophylaxis of bleeding in non haemophiliacs with acquired inhibitors to factors VIII, XI, XII.

In one case FEIBA was successfully used in patient with an inhibitor, suffering from von Willebrand's disease.
FEIBA was also used in combination with Factor VIII concentrate for a continual long term therapy to achieve a complete and permanent elimination of the F VIII inhibitor so as to allow for regular treatment with F VIII concentrate as in patients without inhibitor.

POSOLOGY AND METHOD OF ADMINISTRATION

1. Dosage

Treatment should be initiated and supervised by a physician experienced in the management of hemophilia.

The dosage and duration of the therapy depend on the severity of the disorder of haemostasis, on the location and extent of the bleeding and on the clinical condition of the patient.

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

As a general guide a dose of 50 to 100 U of FEIBA per kg body weight (bw) is recommended, however, 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. See SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE.

Coagulation tests such as the whole blood clotting time (WBCT), the thromboelastogramme (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.

1.1. Spontaneous Haemorrhage

Joint, Muscle and Soft Tissue Haemorrhage

For minor to moderate bleedings 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 mobilization 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 to be given every 6 hour 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. (Do not exceed the maximum daily dose of 200 U/kg bw.)

Other Severe Haemorrhages

Severe haemorrhages, such as CNS bleedings 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. (Do not exceed the maximum daily dose of 200 U/kg bw.)

1.2. Surgery

Taking care not to exceed the maximum daily dose, 50-100 U/kg bw should be given at intervals of up to 6 hours.

1.3. Bleeding prophylaxis in haemophilia A patients with inhibitors during immune tolerance therapy (ITT) or if ITT falls

In high responder patients with a history of frequent bleeding, FEIBA can be given concomitant to F 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.*

* 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°C.

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.

2. Administration

Reconstitute the product as described under INSTRUCTIONS FOR USE and inject or infuse slowly by the intravenous route. Do not exceed an injection/infusion rate of 2 U/kg bw per minute.
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.
It is recommended that every time FEIBA is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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 whole blood clotting time (WBCT) and the aPTT may not correlate with clinical improvement.

CONTRAINDICATIONS

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

- Hypersensitivity to the product
- Disseminated Intravascular Coagulation (DIC):

- Laboratory and/or clinical symptoms which are clearly indicative of DIC.
- Laboratory, histological and/or clinical signs 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 is only indicated in life-threatening bleeding episodes.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

1. Special 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.

When considering re-exposure to FEIBA in patients with known or suspected hypersensitivity to the product, 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 agents.
Minor reactions may be controlled by antihistamines. In case of shock, the current medical standards for shock treatment are to be observed.
As the quantity of sodium in the maximum daily dose may exceed 200 mg, special care should be taken with individuals on a low sodium diet.

Risk of 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 septicemia) for thromboembolic events. Concomitant treatment with recombinant Factor VIIa may increase the risk of developing a thromboembolic event.
The possible presence of such risk factors should always be considered in patients with congenital and acquired hemophilia.
FEIBA should be used with particular caution in patients at risk of DIC, arterial or venous thrombosis.
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. Consider the benefits and risks if FEIBA must be used in a patient receiving emicizumab prophylaxis. If treatment with FEIBA is considered required for patients receiving emicizumab, patients must be closely monitored by their physicians.

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

Monitoring of Therapy
Single dose of 100U/kg bw and daily dose of 200 U/kg bw 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.
In case of significant clinical 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 results indicative of DIC are decreased fibrinogen values, decreased platelet count, and/or presence of fibrin/fibrinogen degradation products (FDP). Other indications of DIC include significantly prolonged thrombin time, prothrombin time, or aPTT.

Non-Haemophilic Patients

Non-haemophilic patients with acquired inhibitor against factors VIII, XI or XII may have both, a bleeding tendency and an increased risk of thrombosis at the same time.

Laboratory Tests and Clinical Efficacy
In vitro tests to control efficacy such as aPTT, whole blood clotting time (WBCT), and thromboelastogramme (TEG) may not correlate with clinical improvement. For this reason, attempts to normalize 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 over dosage.
Significance of Platelet Count
In case of inadequate response to treatment with FEIBA it is recommended to perform a platelet count, since a sufficient number of functionally intact platelet is considered necessary for the efficacy of FEIBA.

2. Special Warnings
Viral Safety
Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, [e.g., 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.

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.
The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for the nonenveloped viruses HAV. The measures taken may be of limited value againt 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. in hemolytic anaemia)
Appropriate vaccination (against hepatitis A and B) should be considered for patients in regular/repeated receipt of plasma-derived products including FEIBA.
It is recommended that every time FEIBA is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

PRECAUTIONS
• 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.
• 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.
• 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).
• The amount of sodium in the maximum daily dose may exceed the recommended daily allowance of dietary sodium for patients on a low sodium diet. In these patients, the amount of sodium from the product should be calculated and taken into account when determining dietary sodium intake.
FEIBA 500 U/1000 U contains approximately 80 mg sodium (calculated) per vial
FEIBA 2500 U contains approximately 200 mg sodium (calculated) per vial
• The recording of the product name and batch number is strongly recommended following each administration of this product in order to be able to identify the batch of product received.
Pediatrics
• Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age.

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 aminocarpoic 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, according to available in vitro data and clinical observations a potential drug interaction may occur (potentially resulting in adverse events such as a thromboembolic event.)
Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab when FEIBA was used as part of a treatment regimen for breakthrough bleeding.

PREGNANCY AND LACTATION
There are no adequate data from the use of FEIBA in pregnant or lactating women.
No animal reproduction studies have been conducted with FEIBA.
Physicians 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, and several complications of pregnancy that are associated with an increased risk of DIC.
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.
See special warning for information on Parvovirus B19 infection

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There are no indications that the product may impair the ability to drive or to operate machines.

ADVERSE REACTIONS

1. **Adverse Reactions From Clinical Trials**

The adverse reactions presented in this section have been reported from 2 studies with FEIBA for the treatment of bleeding episodes in pediatric and adult patients with hemophilia A or B and inhibitors to factors VIII or IX. One study also enrolled acquired hemophilia patients with factor VIII inhibitors (2 of 49 patients).

Adverse Reactions From Clinical Trials	
System Organ Class (SOC)	**Preferred MedDRA (version 18.0)Term**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Increase of inhibitor titer (anamnestic response)*,[a]
IMMUNE SYSTEM DISORDERS	Hypersensitivity[c]
NERVOUS SYSTEM DISORDERS	Somnolence* Dizziness[b] Dysgeusia* Headache[c]
VASCULAR DISORDERS	Hypotension[c]
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Dyspnea*
GASTROINTESTINAL DISORDERS	Nausea*
SKIN AND SUBCUTANEOUS	Rash[c]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills* Pyrexia* Chest pain* Chest discomfort*
INVESTIGATIONS	Hepatitis B surface antibody positive[c]

* A precise estimate of the rate of these adverse reactions is not possible from the available data. ADR reported in the original studies (Hilgartner 1983, 2003; Sjamsoedin LJ. et al.,1981) only.

[a] Increase of inhibitor titer (anamnestic response) [not a MedDRA PT] is the rise of previously existing inhibitor titers occurring after the administration of FEIBA. See Section SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE.

[b] ADR reported in the original studies (Hilgartner 1983, 2003; Sjamsoedin LJ. et al.,1981) and prophylaxis study(090701). Frequency shown is from the prophylaxis study.

[c] ADR reported in the prophylaxis study(090701). Frequency shown is from the prophylaxis study only.

2. Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Disseminated intravascular coagulation

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction

NERVOUS SYSTEM DISORDERS: Paresthesia, Thrombotic stroke, Embolic stroke

CARDIAC DISORDERS: Myocardial infarction, Tachycardia

VASCULAR DISORDERS: Thrombosis, Venous thrombosis, Arterial thrombosis, Hypertension, Flushing

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Pulmonary embolism, Bronchospasm, Wheezing, Cough

GASTROINTESTINAL DISORDERS: Vomiting, Diarrhea, Abdominal discomfort

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema, Urticaria, Pruritus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Malaise, Feeling hot, Injection site pain

OVERDOSE

Some reported thromboembolic events have occurred with doses above 200 U/kg. If signs or symptoms of thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated. See section SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE.

INCOMPATIBILITIES

No compatibility studies have been performed with the product. Therefore, FEIBA must not be mixed with other medicinal products or solvents 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.
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 injection/infusion devices may be used with FEIBA.

INSTRUCTIONS FOR USE/HANDLING/DISPOSAL

FEIBA is to be reconstituted just prior to administration. Aseptic technique should be used throughout the entire reconstitution process and the solution should then be used immediately (as the preparation contains no preservatives).
Swirl gently until all material is dissolved. Ensure that FEIBA is completely dissolved; otherwise, active material will not 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 turbid or have deposits.
Any unused solution must be discarded appropriately.
Mixing of FEIBA with other products or substances must be avoided. It is advisable to flush venous access lines with isotonic saline prior to and after infusion of FEIBA.
If devices other than those supplied with FEIBA are used, ensure use of an adequate filter.

Reconstitution of dried substance:

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).

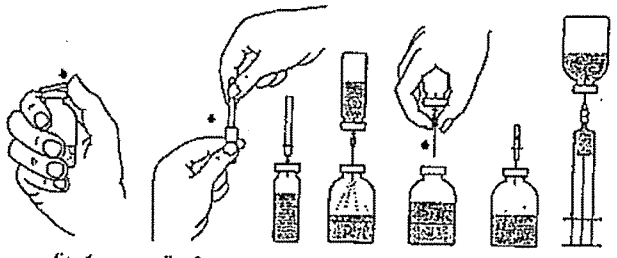
2. Remove protective caps from the concentrate vial and solvent vial (fig. 1) and disinfect the rubber stoppers of both.
3. Remove protective covering from one end of the supplied "transfer needle" by twisting and pulling (fig. 2). Insert the exposed needle through the rubber stopper of the solvent vial (fig. 3).
4. Remove 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 concentrate vial, and insert the free end of the transfer needle through the rubber stopper of the concentrate vial (fig. 4). The solvent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing the needle from the concentrate vial (fig. 5). Gently agitate or rotate the concentrate vial to accelerate dissolution.
7. Upon complete reconstitution of the concentrate, insert the enclosed "aeration needle" provided (fig. 6) and any foam will collapse. Remove aeration needle.

Injection/Infusion:

1. Remove 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 administered by infusion, a disposable infusion set with adequate filter is to be used.

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



SHELF LIFE

The freeze-dried product has a shelf life of two years.
Chemical and physical stability of the reconstituted product has been demonstrated for 3 hours at 20-25°C.
Considering microbiological aspects, FEIBA should be used immediately after reconstitution.
Reconstituted product must not be returned to the refrigerator.

Special Precautions for Storage

Store at 2-8°C. Do not freeze.
Keep container in the outer carton.
Within the indicated shelf life the product may be stored at room temperature (max. +25°C) for a period of up to 6 months. No data are available on the effect of a subsequent (second) storage period at 2-8°C. The start of room temperature storage should be noted on the package.
Store out of the reach of children.

Manufactured by: Takeda Manufacturing Austria AG
Vienna, Austria
Imported by: Takeda (Thailand), Ltd.
Bangkok, Thailand

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ขอรับรองว่าเอกสารกำกับยาหน้า 1-10
ข้อความอื่นเหมือนเดิมที่เคยได้รับอนุมัติไว้ ยกเว้นการแก้ไขตามภาคผนวก ก ข้อ 1 เท่านั้น