

PRODUCT MONOGRAPH

FEIBA NF

Anti-Inhibitor Coagulant Complex, Vapor Heated and Nanofiltered,
Freeze-Dried Substance with Solvent for
Intravenous Injection or Infusion

Human Plasma Fraction with Factor VIII Inhibitor Bypassing Activity

Freeze-Dried Powder, 350-650 Units per 20 mL, 700-1300 Units per 20 mL,
1750-3250 Units per 50 mL

Hemostatic

Shire Pharma Canada ULC
22 Adelaide Street West, Suite 3800
Toronto Ontario M5H 4E3

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection or Infusion	350-650 Units/20ml 700-1300 Units/20ml 1750-3250 Units/50ml	Sodium Chloride and Trisodium Citrate

DESCRIPTION

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered FEIBA NF, is a freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity. *In vitro*, FEIBA NF shortens the activated partial thromboplastin time (aPTT) of plasma containing Factor VIII inhibitor. Factor VIII inhibitor bypassing activity is expressed in arbitrary units. One FEIBA Unit of activity is defined as that amount of FEIBA NF which shortens the aPTT of a high titer Factor VIII inhibitor reference plasma to 50% of the blank value.

FEIBA NF contains Factors II, IX, and X, mainly non-activated, and Factor VII mainly in the activated form. The product contains approximately equal unitages of Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors. In addition, 1 -6 units of Factor VIII coagulant antigen (F VIII C: Ag) per mL are present. The preparation contains only traces of factors of the kinin generating system. It contains no heparin.

Reconstituted FEIBA NF contains 4 mg of trisodium citrate x 2 H₂O and 8 mg of sodium chloride per mL.

FEIBA NF has been prepared from Source Plasma and/or Fresh Frozen Plasma. Individual donations of human plasma are combined to form plasma pools. Prior to being used for manufacture of FEIBA NF, each plasma pool is tested for the presence of genome sequences of the human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Parvovirus B19 (B19V) using PCR

To prevent the transmission of infective agents by the administration of FEIBA NF, prescribed manufacturing procedures utilized at the plasma collection centers and plasma testing laboratories are designed to reduce the risk of transmitting viral infections. They include measures taken for donor and plasma selection **, as well as virus removal and inactivation steps during manufacturing.

** All plasma units used for manufacture are ALT tested and non-reactive in tests for HBs-antigen and antibodies to HCV, HIV-1 and HIV-2. Before further processing all individual plasma donations are subjected to an inventory hold for a possible look-back of plasma donations suspected of infection.

INDICATIONS AND CLINICAL USE

FEIBA NF (Anti-Inhibitor Coagulant Complex) is indicated for use in Hemophilia A and B patients with inhibitors for:

- Control of spontaneous bleeding episodes
- Surgical interventions
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children older than 6 years of age

Treatment should be initiated and supervised by a healthcare practitioner experienced in the use of coagulation agents and in the management of bleeding disorders. FEIBA NF may be used for treating non-haemophiliacs with acquired inhibitors to factors VIII, XI and XII in case of life-threatening haemorrhages⁵⁻¹². One case has been reported where FEIBA NF was effective in a patient with von Willebrand's disease with an inhibitor¹⁶.

Clinical experience suggests that patients with a Factor VIII inhibitor titer of less than 5 B.U. may be successfully treated with Antihemophilic Factor. Patients with titers ranging between 5 and 10 B.U. may either be treated with Antihemophilic Factor or FEIBA NF. Cases with Factor VIII inhibitor titers greater than 10 B.U. have generally been refractory to treatment with Antihemophilic Factor.

Guidelines to First and Second Choice Treatment:

AICC = Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF

AHF = Antihemophilic Factor

Patient's Inhibitor Titer	Clinical Situation		
	Minor Bleeding	Major Bleeding	Surgery (Emergency)
less than 5 B.U.	AHF	AHF	AHF
5 to 10 B.U.	AHF AICC	AHF AICC	AHF AICC
more than 10 B.U.	AICC	AICC	AICC

Inadequate response to treatment may result from an abnormal platelet count or impaired platelet function¹³⁻¹⁵ which were present before treatment with FEIBA NF.

CONTRAINDICATIONS

The use of Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF is contraindicated in patients who are known to have a normal coagulation mechanism and in patients who have hypersensitivity to the product.

It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis. In patients with a tentative or definite diagnosis of coronary heart disease as well as in patients with acute thrombosis and/or embolism (including myocardial infarction) the use of FEIBA NF is only indicated in life-threatening bleeding events.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA, particularly following the administration of high doses and/or in patients with thrombotic risk factors (see WARNINGS AND PRECAUTIONS AND ADVERSE EVENTS).

General

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF must be used only in patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies. It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis.

FEIBA should be used with particular caution in patients at risk of DIC, arterial or venous thrombosis

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

Thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA. Many 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 (e.g. patients in the postoperative state or with liver disease, infection, inflammation, cancer, angina pectoris or myocardial infarction). 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 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). Allergic Reactions should be treated with antihistamines and glucocorticoids. In the case of shock medical attention should be initiated as appropriate. Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported.

At first signs or symptoms 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 patients hypersensitivity (allergic or nonallergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.

Single doses of 100 units per kg bodyweight of Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF and daily doses of 200 units per kg bodyweight of FEIBA NF should not be exceeded.

High doses of FEIBA NF 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 DIC are decreased fibrinogen, decreased platelet count, and/or presence of fibrin-fibrinogen degradation products (FDP). Other indications of DIC include significantly prolonged thrombin time, prothrombin time, or partial thromboplastin time.

Tests used to control efficacy such as aPTT, WBCT, and TEG do not correlate with clinical improvement. For this reason, attempts at normalizing these values by increasing the dose of FEIBA NF may not be successful and are strongly discouraged because of the potential hazard of producing DIC by overdosage.

This product is manufactured using components of human blood, which may contain the causative agents of hepatitis and other viral diseases. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include

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

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for nonenveloped viruses such as 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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hemolytic anemia).

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

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 bypassing agent, use of another agent should be considered.

Anamnestic response with rise in Factor VIII inhibitor titer has been observed in 20% of the cases (see CLINICAL PHARMACOLOGY). 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 a 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.

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.

No animal reproduction studies have been conducted with FEIBA.

The effects of FEIBA on fertility have not been established.

Pregnant Women:

Pregnancy Category C

The safety of FEIBA NF during pregnancy and lactation has not been established. Pregnancy and postpartum period is characterized by an increased risk of thrombosis, and several complications of pregnancy are associated with an increased risk of DIC. FEIBA NF should be given to a pregnant woman only if clearly needed.

Pediatrics

- Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years for the control of spontaneous bleeding episodes and surgical interventions
- No data are available in children younger than 6 years regarding the use of FEIBA NF for routine prophylaxis
- No data are available regarding the use of FEIBA NF in newborns

Geriatrics

No specific data is available on the use of FEIBA in the geriatric population.

Monitoring and Laboratory Tests

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 the drug substance is available. Coagulation tests such as whole blood clotting time (WBCT), and the aPTT may not correlate with clinical improvement.

Global hemostatic tests such as thromboelastogram (TEG) or Thrombin Generation Assay (TGA) may be useful tools to monitor and optimize the treatment; however, they are currently considered exploratory.²⁰

ADVERSE REACTIONS

After application of high doses (single infusion of beyond 100 units per kg of weight, and daily doses of 200 units per kg of body weight) of Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA NF, laboratory and/or clinical signs of DIC have occasionally been observed.

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

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 (4 of 49 patients).

Adverse Reactions From Clinical Trials			
System Organ Class (SOC)	Preferred MedDRA (version - 18.0)Term	Frequency Category	Frequency Ratio (Percentage) n=36
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Increase of inhibitor titer (anamnesic response)*, ^a	Unknown	-
IMMUNE SYSTEM DISORDERS	Hypersensitivity^c	Common	1/36 (2.8)
NERVOUS SYSTEM DISORDERS	Somnolence[*] Dizziness^b Dysgeusia[*] Headache^c	Unknown Common Unknown Common	- 1/36 (2.8) - 1/36 (2.8)
VASCULAR DISORDERS	Hypotension^c	Common	1/36 (2.8)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Dyspnea[*]	Unknown	-
GASTROINTESTINAL DISORDERS	Nausea[*]	Unknown	-
SKIN AND SUBCUTANEOUS	Rash^c	Common	1/36 (2.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills[*] Pyrexia[*] Chest pain[*] Chest discomfort[*]	Unknown Unknown Unknown Unknown	- - - -
INVESTIGATIONS	Hepatitis B surface antibody positive^c	Common	3/36 (8.3)

Legend: ADR frequency is based upon the following scale: Very Common ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), Very Rare ($< 1/10,000$)

* 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; Sjamssoedin LJ. et al.,1981) only.

^a Increase of inhibitor titer (anamnesic response) [not a MedDRA PT] is the rise of previously existing inhibitor titers occurring after the administration of FEIBA.

^b ADR reported in the original studies (Hilgartner 1983, 2003; Sjamssoedin 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.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during post marketing period. The frequency cannot be estimated due to the nature of the data and therefore is categorized as unknown:

System organ classes according to MedDRA	Preferred MedDRA term (version -18.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Disseminated intravascular coagulation (DIC)
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 Broncospasm 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

*Myocardial infarctions occurred after the administration of doses above the maximum daily dose and/or prolonged application and/or the presence of risk factors for thromboembolism.

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.

DRUG INTERACTIONS

Overview

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

The possibility of thromboembolic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA.

In cases of concomitant rFVIIa use, 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.)

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 plastic injection/infusion devices should be used with FEIBA.

Drug-Drug Interactions

Interactions with other drugs have not been established.

No compatibility studies have been performed with the product. Therefore, FEIBA must not be mixed with other medicinal products or solvents.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Lifestyle Interactions

There is no information of the effects of FEIBA on the ability to drive or operate an automobile or other heavy machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Clinical trials⁵⁻⁷ have demonstrated that the response to treatment with Anti-Inhibitor Coagulant FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

Complex, Vapor Heated, and Nanofiltered FEIBA NF, may differ from patient to patient with no correlation to the patient's inhibitor titer. Response may also vary between different types of hemorrhage (e.g. joint hemorrhage vs. CNS hemorrhage).

Recommended Dose and Dosage Adjustment

As a general guideline a dosage range of 50 to 100 FEIBA Units of FEIBA NF per kg of body weight is recommended. However, care should be taken to distinguish between the following indications, all of which have undergone careful clinical evaluation:

Table 1
Recommended Dose and Dosing Adjustment

Indication	Dose	Frequency and Duration
Joint Hemorrhages	50-75 U/kg of body weight	<ul style="list-style-type: none">• 12 hour intervals• dose can be increased to 100 U/kg of body weight 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.• A daily dosage of 200 units per kg of body weight should not be exceeded.
Mucous Membrane Bleeding	50 U/kg of body weight	<ul style="list-style-type: none">• 6-hour intervals under careful monitoring (visible bleeding site, repeated measurements of the patient's hematocrit)• If higher dosages are given, take care to prolong dosage intervals so as to make certain that a maximum daily dosage of 200 units per kg of body weight is not exceeded.
Soft Tissue Hemorrhage (i.e. retroperitoneal bleeding)	100 U/kg of body weight	<ul style="list-style-type: none">• 12-hour intervals are recommended• A daily dosage of 200 units per kg of body weight should not be exceeded.
Other Severe Hemorrhages (i.e. CNS bleedings)	100 U/kg of body weight	<ul style="list-style-type: none">• 12-hour intervals• When, in order to achieve a clear clinical improvement, the dosage intervals must be shortened, it is to be ensured that a daily dosage

		of 200 units per kg of body weight is not exceeded.
Surgery	50-100 U/kg of body weight	<ul style="list-style-type: none"> • 6 hours intervals are recommended • A maximum daily dose of 200 U/kg body weight should not be exceeded
Routine Prophylaxis (prevention of bleeding episodes)	85±15 U/kg of body weight (70 to 100 U/kg of body weight)	<ul style="list-style-type: none"> • Every other day • 3-4 times weekly • Adjust dose based on the patient's clinical response

* 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

Reconstitution

Instructions for use for BAXJECT II Hi-Flow:

Reconstitution of powder to prepare a solution for injections

Use aseptic technique throughout entire procedure.

1. Warm the unopened vial containing the solvent (Sterile Water for Injection, EP) to room temperature if necessary, e.g. using a sterile water bath for warming within several minutes (max. +37°C).
2. Remove the protective caps from the FEIBA vial and solvent vial and cleanse the rubber stoppers with germicidal solution of both and allow to dry. 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 gently until all the material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

Fig. a



Fig. b



Fig. c

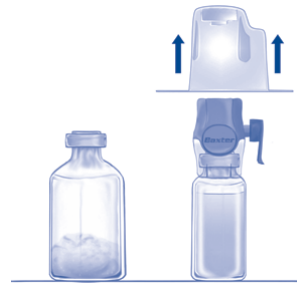


Fig.d



Injection/Infusion

Use aseptic technique throughout entire procedure.

1. Remove the blue cap from BAXJECT II Hi-Flow. Take the syringe and connect it to BAXJECT II Hi-Flow (DO NOT DRAW AIR INTO THE SYRINGE) (Fig. e).
2. Invert the system (with FEIBA vial on top). Draw the FEIBA solution into the syringe by pulling the plunger back slowly (Fig. f).
3. Disconnect the syringe.
4. Slowly inject the solution intravenously with a winged set for injection.

Fig. e



Fig. f



Do not exceed an infusion rate of 2 U FEIBA/kg/Body Weight per minute.
Do not refrigerate after reconstitution!

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

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.

After complete reconstitution of FEIBA NF its injection or infusion should be commenced as promptly as practicable, but must be completed within three hours following reconstitution.

The solution must be given by intravenous injection or intravenous drip infusion and the maximum injection or infusion rate must not exceed 2 units per kg of body weight per minute. In a patient with a body weight of 75 kg, this corresponds to an infusion rate of 2.5 - 7.5 mL per minute depending on the number of units per vial (see label on vial).

OVERDOSAGE

Some of the reported thromboembolic events 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Anamnestic response is an increase in inhibitor titer of preexisting inhibitors (antibodies) in some patients. FEIBA contains FIX and trace amounts of FVIII; which elicit a secondary immune response leading to an increase in inhibitor titer. Anamnestic response is generally transient and the titers decrease over time with continued regular use of FEIBA. The efficacy of FEIBA is not impacted by the increase in inhibitor titer.

Mechanism of Action

The components of the activated prothrombin complex, zymogen prothrombin (F II) and activated Factor X (FXa) play the crucial role in the action of FEIBA. The other zymogens and active enzymes enhance the thrombin generation process on the activated platelet surface thus achieving hemifostasis bypassing the requirements of factor VIII (or FIX).

Pharmacokinetics

Since FEIBA NF 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 NF.

STORAGE AND STABILITY

FEIBA NF can be stored refrigerated or at room temperature (between 2°C to +25°C) for the entire shelf-life of the product.

Avoid freezing, which may damage the diluent bottle.

FEIBA NF must not be used beyond the expiry date indicated on the label.

SPECIAL HANDLING INSTRUCTIONS

Reconstituted Solutions

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF is to be reconstituted only immediately before administration. The solution should then be used promptly. Any unused solution must be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered FEIBA NF is supplied as freeze-dried powder, accompanied by a suitable volume of Sterile Water for Injection, E. P. and a Baxject II Hi-Flow device.

The number of FEIBA Units of Factor VIII inhibitor bypassing activity is stated on the label of each bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Factor Eight Inhibitor Bypassing Activity
Chemical name:	Not applicable
Molecular formula and molecular mass:	Not applicable
Structural formula:	<p>FEIBA is comprised of the zymogen forms of the procoagulant factors FII, FVII, FIX, FX, and the anticoagulant protein C in a physiologically balanced ratio, approximately 1 U/1 U FEIBA. FEIBA contains trace amounts of the activated form of factors II, IX and X 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.³²</p> <p>Human blood coagulation factors II, VII, IX and X as well as their activated forms are glycoproteins characterized by 10 - 12 gamma-carboxylated glutamic acid residues, located in the amino terminal region of the zymogens, and a serine protease region.</p>
Physicochemical properties:	Not applicable

Product Characteristics

FEIBA NF is an Anti-Inhibitor Coagulant Complex (AICC). Its activity is based on its so-called "Factor Eight Inhibitor Bypassing Activity", i.e. activating the clotting cascade by multiple reactions, and thus achieving hemostasis even in the absence of factor VIII (or FIX).

Viral Inactivation

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 of viruses. The manufacturing process of FEIBA NF includes a nanofiltration step and a two-step vapour heat treatment for virus inactivation and virus reduction. The nanofiltration is performed using a subsequent filtration through 75 nm and 35 nm filters. The vapour heat treatment is conducted for 10 hours at $60^{\circ} \pm 0.5^{\circ}\text{C}$ with excess pressure of 190 ± 25 mbar followed by 1 hour at $80^{\circ} \pm 0.5^{\circ}\text{C}$ with excess pressure of 375 ± 35 mbar.

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 and parvovirus B19.

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

CLINICAL TRIALS

A clinical study⁴ testing Antihemophilic Factor treated by a similar vapor heating procedure has shown none of 4 lots used in the study to produce nonA, nonB hepatitis in intensively followed patients naïve to blood product administration.

The safety and efficacy of FEIBA VH has been demonstrated by two prospective clinical trials⁵⁻⁷. The first, conducted by Sixma and collaborators during 1979 and early 1980, was a randomized double-blind study comparing the effect of FEIBA VH and PROTHROMPLEX IMMUNO (a non-activated prothrombin complex concentrate) in 15 patients with haemophilia A and inhibitors to Factor VIII. A total of 150 bleeding episodes (primarily joint and musculoskeletal plus a few mucocutaneous) were treated. A single dose of 88 FEIBA Units per kg of body weight was used uniformly for treatments with FEIBA VH. The study showed that, based on subjective patient evaluation, FEIBA was fully effective in 41.0% and partly effective in 24.6% of episodes (i.e. combined effectiveness of 65.6%), while PROTHROMPLEX IMMUNO was rated fully effective in 25.0% and partly effective in 21.4% of episodes (i.e. combined effectiveness of 46.4%).

The second study with FEIBA was a multiclinic study conducted by Hilgartner *et al.* It was designed to evaluate the efficacy of FEIBA in the treatment of joint, mucous membrane, musculocutaneous and emergency bleeding episodes such as central nervous system hemorrhages and surgical bleedings. In 49 patients with inhibitor titres of greater than 5 Bethesda Units (from nine cooperating haemophilia centers), 489 single doses were given for the treatment of 165 bleeding episodes. The usual dosage was 50 FEIBA Units per kg of body weight, repeated at 12-hour intervals (6-hour intervals in mucous membrane bleedings), if necessary. Bleeding was controlled in 153 episodes (93%). In 130 (78%) of the episodes hemostasis was achieved with one or more infusions within 36 hours. Of these, 36% were controlled with one infusion within 12 hours. An additional 14% of episodes responded after more than 36 hours.

Of the 489 single doses only 18 (3.7%) caused minor transient reactions in recipients. 10 out of 49 patients (20%) showed a rise in their inhibitor titers. In 5 of these patients (10%) the rise was tenfold or more. However, of these 10 patients 3 had received Factor VIII or Factor IX concentrates within 2 weeks prior to treatment with FEIBA. These anamnestic rises have not been observed to interfere with the efficacy of Anti-Inhibitor Coagulant Complex, FEIBA.

Routine Prophylaxis Study²⁵

A multicenter, open-label, prospective, randomized, parallel clinical study was conducted to compare FEIBA NF prophylaxis to on-demand treatment. Thirty six (36) hemophilia subjects (33 hemophilia A and 3 hemophilia B) with inhibitors refractory to Factor VIII or FIX treatment were analyzed in the primary analysis set (intent-to-treat). Subjects were randomized to receive 12 months \pm 14 days of prophylactic or on-demand treatment with FEIBA NF. Seventeen (17) subjects were randomized to the prophylaxis arm and received 85 ± 15 U/kg of FEIBA NF every other day. Nineteen (19) subjects were randomized to the on-demand arm and received FEIBA NF for the treatment of acute bleeding episodes per the dose and dosing regimen recommended by the investigator. All subjects were being treated on an on-demand basis at study entry. Inclusion criteria were subjects with a history of high titer inhibitors or low titer refractory to increased factor VIII or IX dosing, age range between 4 and 65, and subjects receiving bypassing agents with ≥ 12 bleeds in the 12 months prior to trial entry. Subjects with a history of thromboembolic events, symptomatic liver disease, or a platelet count $< 100,000$ per mL, and those receiving immune tolerance induction or routine prophylaxis were excluded.

The study population included 4 subjects ≥ 7 to < 12 years, 5 subjects ≥ 12 and < 16 years and 27 subjects ≥ 16 years. A total of 825 bleeding episodes were reported including 196 in the prophylaxis arm and 629 in the on-demand arm.

Hemostatic efficacy for the treatment of acute bleeds was evaluated. The following table shows the number of infusions needed to control the bleeding by treatment group.

Table 2
Distribution of the Number of Bleeding Episodes Resolved with 1, 2, or greater than 2
Infusions by Treatment Regimen
(Study 090701: Additional Evaluations for Bleeding Episodes Analysis Set)

Treatment Regimen	Number of infusions used to control bleeds					
	1 infusion ^a		2 infusions ^a		≥3 infusions ^a	
	Number of subjects	Number (%) of BEs	Number of subjects	Number (%) of BEs	Number of subjects	Number (%) of BEs
Prophylaxis	11	98 (56.6)	13	41 (23.7)	7	34 (19.7)
On-Demand	19	352 (56.5)	16	134 (21.5)	14	137 (22.0)

Abbreviations: BEs=bleeding episodes.

^a Results presented by number of infusions (1, 2, and ≥3) are mutually exclusive.

The overall median annual bleeding (ABR) rate (range) was 7.9 (0-43.9) for subjects on prophylaxis treatment compared to 28.7 (5.8-76.3) with on-demand treatment corresponding to a reduction of 72.5% in the median bleeding rate.

An analysis adjusting for the time subjects remained on study showed that the estimated mean bleeding rate was 12.1 for subjects receiving prophylaxis treatment and 33.5 for subjects receiving on-demand treatment. A comparison of the two treatment groups showed that the estimated mean bleeding rate was 2.8 times greater for subjects receiving on-demand treatment than for subjects receiving prophylaxis (p=0.0003).

Zero bleeding episodes were achieved on prophylaxis in 2/17 (11.8%) subjects in the intent-to-treat analysis sets. None of the on-demand subjects achieved zero bleeding episodes during the study.

Table 3 shows ABRs by bleed type and etiology between prophylaxis and on-demand regimens.

Table 3
Median (IQR) ABRs by Bleeding Etiology and Type (efficacy ITT analysis set)

Etiology	Median (IQR) ABR ^a	
	Prophylaxis (n=17)	On-Demand (n=19)
Spontaneous ^b	5.6 (5.1)	18.9 (32.6)
Traumatic	2.5 (3.1)	4.7 (8.7)
Joint	6.0 (7.1)	22.9 (32.8)
Non-Joint	0.5 (2.0)	2.9 (4.0)
Spontaneous Joint	4.5 (5.1)	16.6 (30.9)
Spontaneous Non-Joint	0 (1.0)	1.0 (2.0)
Traumatic Joint	1.0 (3.1)	4.0 (6.1)
Traumatic Non-Joint	0 (1.0)	0 (1.9)

^a Abbreviations: ABR = annualized bleeding episode rate, IQR – Inter Quartile Range. IQR is defined as the difference between the 75th percentile (3rd quartile) and the 25th percentile (first quartile).^b Spontaneous includes unknown/undetermined etiology.

ABR by age category between prophylaxis and on-demand regimens is provided in Table 4.

Table 4
ABRs by Age Category for Prophylaxis vs. On-Demand Treatment (N=36)
(Study 090701:Intent-to-Treat Efficacy Analysis Set)

Age Category	Prophylaxis N=17		On-Demand N=19	
	Number of Subjects	ABR Median	Number of Subjects	ABR Median
Children (>=7 to <12 years old)	2	7.7	2	39.3
Adolescent ^a (>=12 to <16 years old)	3	27.5	2	30.9
Adult (>=16 years old)	12	6.9	15	23.9
All	17	7.9 (8.1) ^b	19	28.7 (32.3) ^b

Abbreviations: ABR = annualized bleeding episode rate

^a One adolescent subject on prophylaxis had a higher rate of bleeding due to increased physical activity after study enrollment.

^b Interquartile-range.

Table 5 indicates the number of new target joints as well as annualized bleeding episodes in new target joints between on-demand and prophylaxis regimens. Target joints are defined as ≥ 4 bleeding episodes within 6 months. In this study, ankles, knees, elbows and hips were considered as possible target joint locations. Preexisting target joints were not considered as new target joints.

Table 5
Summary of New Target Joints: ABR and Number of New Target Joints

Statistic	Prophylaxis (n=17)	On-Demand (n=19)
Number of Subjects with New Target Joints	5	11
Number of New Target Joints	7	23
Number of New Target Joint Bleeding Episodes	46	243
ABR Target Joint Median (IQR) ^a	0.0 (4.1)	5.9 (12.9)

^a Abbreviations: ABR = annualized bleeding episode rate, IQR= Interquartile Range. IQR is defined as the difference between the 75th percentile (3rd quartile) and the 25th percentile (first quartile).

The results of the study demonstrate the safety and effectiveness of FEIBA prophylaxis in reducing the overall bleeding episode rate.

DETAILED PHARMACOLOGY

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF, is an activated prothrombin complex preparation. Although Anti-Inhibitor Coagulation Complex, Vapor Heated, and Nanofiltered, FEIBA NF, contains the coagulation factors of the prothrombin complex, it differs from the non-activated preparations in that it contains high quantities of FEIB-Activity (Factor VIII Inhibitor Bypassing Activity), which is expressed in arbitrary units, depending on the manufactured lot.

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF, has been developed for the treatment of patients with inhibitors to coagulation factors, in particular patients with inhibitors to factor VIII in whom factor VIII-preparations have a limited efficacy. Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF, has been shown to correct defective coagulation in that its FEIB-Activity bypasses the inhibitor, initiating the clotting mechanism in a stage where factor VIII is no longer required. The mechanism which produces the bypass has been investigated *in vitro* by several authors^{2,3,17-19}.

Some of the preclinical investigations were initiated and conducted only after Anti-Inhibitor Coagulant Complex, FEIBA, had already been administered successfully in patients with defective coagulation systems and inhibitors. The early use in humans seemed to be justified because the composition of Anti-Inhibitor Coagulant Complex, FEIBA, as an activated prothrombin complex preparation, differed only slightly from that of non-activated prothrombin complex preparations. Another argument in support of clinical use was the absence of an adequate animal model that would be comparable with Factor VIII inhibitor patients, and this holds true up to this very moment. When preclinical studies were conducted at a later stage, this was done primarily with the object of characterizing the activated prothrombin complex preparation, which was important also for the future development of the product. It is important to note therefore that both toxicity and thrombogenicity tests were done on animals with normal coagulation systems and do therefore not permit comparison with patient groups for whom activated prothrombin complex preparations are indicated. As with all human blood products multiple use in one and the same animal is not possible because of the antigenicity of the test material.

What has been said about safety tests also holds true for efficacy tests. There are no animal models which could be correlated with the patient groups described above. Investigations in hemophilic dogs cannot be used to evaluate efficacy, as hemophilic patients without inhibitor will not be given Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF. However, the efficacy of FEIBA NF was investigated in different animal models: the quantification of the thrombogenicity of FEIBA NF has been compared in a rabbit stasis model and the efficacy has been investigated in a rabbit bleeding model.

***In Vitro* Tests**

These tests were conducted to demonstrate that Anti-Inhibitor Coagulant Complex, FEIBA VH, has a composition similar to that of non-activated prothrombin complex preparations. The results of the tests performed on eight lots of FEIBA VH, demonstrated that FEIBA VH, contains approximately equal activities of factors II, VII, IX, and X - expressed in units of factors II, VII, IX, and X - and

FEIB-activity, expressed in FEIBA Units. One vial of FEIBA, contains between 440 and 660 FEIBA Units, 550 and 750 Units of factor II, 411 and 809 Units of factor VII, 336 and 871 Units of factor IX, and 480 and 560 Units of factor X. Factor VII activity is present mainly as activated factor VII: between 89 and 98% of the total factor VII activity in FEIBA, is activated factor VII activity.

***In Vivo* Test for Thrombogenic Potential of FEIBA NF**

Three lots of FEIBA NF and three lots of FEIBA VH were tested in a rabbit venous stasis model (Wessler et al., 1959). Six animals were used per group. Each FEIBA preparation was tested in five different doses i.v. (1, 4, 10, 20, and 40 U/kg), to obtain complete dose-response curves. Nearly identical dose-response curves were obtained for both preparations compared, and also for the three compared lots of FEIBA NF and FEIBA VH each.

These results cannot and should not be used to interpret the efficacy of FEIBA. Neither have these data unrestricted validity for safety evaluation, since this is a "venous stasis test" performed in rabbits with normal blood coagulation, and the results therefore cannot be compared to clinical results in inhibitor patients with impaired coagulation systems.

In general, clinical experience has shown FEIBA NF not to produce thrombogenic reactions in dosages of up to 100 FEIBA Units/kg of body weight. In the Wessler Test 4 FEIBA Units/kg of b.w. are not thrombogenic, while higher doses may have thrombogenic effects.

***In Vivo* Test for Efficacy of FEIBA NF**

Three lots of FEIBA NF were compared with one lot of FEIBA VH in a rabbit bleeding model of antibody-induced haemophilia A with factor VIII inhibitor. FEIBA at a dose of 100 FEIBA Units/kg bodyweight or buffer was infused and cuticle bleeding rate was determined in parallel. 30 minutes later, cuticle bleeding rate was measured again. The data were statistically analyzed. No statistically significant difference in the ability to reduce the rate of blood flow at a dose of 100 U FEIBA/kg was found between FEIBA NF and FEIBA VH. At a dose of 100 U FEIBA /kg bodyweight, both products reduced the Factor VIII-inhibitor related increased bleeding rate close to zero, indicating a strong procoagulant activity while the respective buffer control had no effect on the bleeding intensity. This result indicates that the introduction of nanofiltration did not alter the characteristics of the product.

Safety Pharmacology (*In vivo* Test for Anaphylactoid Potential)

The risk of an anaphylactoid reaction, evaluated in a guinea pig model for bronchospasm, after administration of FEIBA NF is at least as unlikely in clinical use as after administration of FEIBA VH.

MICROBIOLOGY

FEIBA NF is a parenteral product and produced under aseptic conditions.

TOXICOLOGY

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

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

Because human plasma proteins are not known to cause tumorigenic or mutagenic effects, experimental studies, particularly in heterologous species, are not considered necessary.

Acute Toxicity (LD₅₀)

For FEIBA NF, two single dose toxicity studies conducted in mice and rats, respectively after intravenous application of FEIBA NF and FEIBA VH indicated no difference in acute toxicity. The No Observed Adverse Effect Level (NOAEL) was determined as 300 U/kg for mice and as 100 U/kg for rats. These animal models, in contrast to patients, have an intact coagulation system and were chosen to represent a worst case scenario.

Further, an *in-vivo* study in rabbits concerning local tolerance indicated equally local tolerance of FEIBA NF and FEIBA VH.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICAL INFORMATION

FEIBA NF

Anti-Inhibitor Coagulant Complex, Vapor Heated and Nanofiltered

Read this carefully before you start **FEIBA NF** administered and each time you use it. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FEIBA NF**.

Serious Warnings and Precautions

Thromboembolic events have been reported during post- marketing surveillance following infusion of FEIBA, particularly following the administration of high doses and/or in patients with thrombotic risk factors (see WARNINGS AND PRECAUTIONS AND ADVERSE EVENTS).

What is FEIBA NF used for?

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered FEIBA NF is indicated for the control of spontaneous bleeding episodes, to cover surgical interventions in haemophilia A and B patients with inhibitors and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children older than 6 years of age with hemophilia A or B with inhibitors.

In addition, FEIBA NF may be used for treating non- haemophiliacs with acquired inhibitors to factors VIII, XI and XII in case of life-threatening haemorrhages⁵⁻¹². One case has been reported where FEIBA was effective in a patient with von Willebrand's disease with an inhibitor¹⁶.

Clinical experience suggests that patients with a Factor VIII inhibitor titer of less than 5 B.U. may be successfully treated with Antihemophilic Factor. Patients with titers ranging between 5 and 10 B.U. may either be treated with Antihemophilic Factor or FEIBA NF. Cases with Factor VIII inhibitor titers greater than 10 B.U. have generally been refractory to treatment with Antihemophilic Factor.

Guidelines to First and Second Choice Treatment:

AICC = Anti-Inhibitor Coagulant Complex, Vapor Heated and Nanofiltered, FEIBA NF

AHF = Antihemophilic Factor

Patient's Inhibitor Titer	Clinical Situation		
	Minor Bleeding	Major Bleeding	Surgery (Emergency)
less than 5 B.U.	AHF	AHF	AHF
5 to 10 B.U.	AHF AICC	AHF AICC	AHF AICC
more than 10 B.U.	AICC	AICC	AICC

Inadequate response to treatment may result from an abnormal platelet count or impaired platelet function¹³⁻¹⁵ which were present before treatment with FEIBA NF.

How does FEIBA NF work?

FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

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FEIBA NF is used for the treatment of hemorrhages in hemophilia A and B patients with inhibitors.

Furthermore, FEIBA NF can be used for the treatment of hemorrhages in non-hemophilic patients who have developed inhibitors to factors VIII, IX and XI.

FEIBA NF has been used in combination with factor VIII concentrate during ITI until eradication of inhibitors.

What are the ingredients in FEIBA NF?

Medicinal ingredients: Anti-Inhibitor Coagulant Complex

Non-medicinal ingredients: Sodium Chloride and Trisodium Citrate

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph

FEIBA NF comes in the following dosage forms:

Anti-Inhibitor Coagulant Complex, Vapor Heated and Nanofiltered, FEIBA NF is supplied as freeze-dried powder, accompanied by a suitable volume of Sterile Water for Injection, E. P., and a Baxject II Hi-Flow device.

The number of FEIBA Units of Factor VIII inhibitor bypassing activity is stated on the label of each bottle (350 – 650 Units per 20ml, 700 – 1300 Units per 20ml, 1750 - 3250 Units per 50ml).

Do not use FEIBA NF if:

The use of Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered FEIBA NF is contraindicated in patients who are known to have a normal coagulation mechanism and in patients who have hypersensitivity to the product.

It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis. In patients with a tentative or definite diagnosis of coronary heart disease as well as in patients with acute thrombosis and/or embolism (including myocardial infarction) the use of FEIBA NF is only indicated in life-threatening bleeding events.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use FEIBA NF.

Other warnings you should know about:

Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered, FEIBA NF must be used only in patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies. It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis.

FEIBA should be used with particular caution in patients at risk of DIC, arterial or venous thrombosis. At first signs or symptoms of Thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

Thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction and stroke, have occurred in the course of treatment with FEIBA. Many 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 (e.g. patients in FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

the postoperative state or with liver disease, infection, inflammation, cancer, angina pectoris or myocardial infarction). 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 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). Allergic Reactions should be treated with antihistamines and glucocorticoids. In the case of shock medical attention should be initiated as appropriate. Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported.

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

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

Anamnestic response with rise in Factor VIII inhibitor titer have been observed in 20% of the cases. Clinical and published data suggests that the efficacy of FEIBA is not reduced.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FEIBA NF:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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

The possibility of thromboembolic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA.

In cases of concomitant rFVIIa use, 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.).

As all other blood coagulation factors, FEIBA should not be mixed with other medicinal products prior to application since this might impair the efficacy and safety of the product.

How to take FEIBA NF:

Reconstitute the freeze-dried FEIBA powder with the enclosed solvent and administer the solution intravenously.

Always use FEIBA exactly as your doctor has instructed you. Please ask your doctor or pharmacist, if you are not entirely sure. Taking into consideration the severity of the blood coagulation disorder, the location and extent of the hemorrhage, and your general condition and response to the preparation, the doctor has determined the dose and dosage intervals required for you personally. Do not change the dosage established by your doctor and do not discontinue the application of the preparation independently.

Warm the product to room or body temperature prior to administration.

FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

FEIBA is to be reconstituted only immediately before administration. The solution should then be used immediately (the preparation does not contain preservatives). Solutions, which are turbid or have deposits, are to be disposed of appropriately. Do not reuse opened containers. Do not use the product, if its sterile barrier system or its packaging is damaged or it shows any sign of deterioration.

Usual dose:

As a general guideline a dosage range of 50 to 100 FEIBA Units of FEIBA NF per kg of body weight is recommended. However, care should be taken to distinguish between the following indications, all of which have undergone careful clinical evaluation:

- Joint haemorrhages
- Mucous Membrane Bleeding
- Soft tissue haemorrhages
- Other severe haemorrhages
- Surgery

A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded.

For prevention of bleeding episodes, dose 85 ± 15 units per kg body weight (70 to 100 units per kg body weight) every other day (3 to 4 times weekly). Dose to be adjusted based on the patient's clinical response.

Overdose:

Some of the reported thromboembolic events 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

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using FEIBA NF?

These are not all the possible side effects you may feel after FEIBA NF administered. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

After application of high doses (single infusion of beyond 100 U/kg of body weight, and daily doses of 200 U/kg bw) of Anti- Inhibitor Coagulant Complex, Vapor-Heated, and Nanofiltered, FEIBA NF, laboratory and/or clinical signs or DIC have occasionally been observed.

As with all human plasma products, any kind of allergic reaction may be seen, ranging from mild, short-term urticarial rashes to severe anaphylactoid reactions.

Administration of FEIBA NF should be discontinued immediately, if such signs appear. Allergic reactions should be treated with antihistamines and glucocorticoids. In the case of shock medical attention should be initiated as appropriate.

If you have trouble, some symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect ;
- eBy calling 1-866-234-2345 (toll-free);
- eBy completing a Patient Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program

Health Canada, Postal Locator 0701E
Ottawa, ON

K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

FEIBA NF can be stored refrigerated or at room temperature (between 2°C to +25°C) for the entire shelf-life of the product.

Avoid freezing, which may damage the diluent bottle.

FEIBA NF must not be used beyond the expiry date indicated on the label.
Keep out of reach and sight of children.

Reconstituted Solutions

Anti-Inhibition Coagulant Complex, Vapor Heated and Nanofiltered, FEIBA NF is to be reconstituted only immediately before administration. The solution should then be used promptly. Any unused solution must be discarded.

Instructions for Using FEIBA NF Instructions for use for BAXJECT II Hi-

Flow:

FEIBA NF [Anti-Inhibitor Coagulant Complex, Vapor Heated, and Nanofiltered]

Reconstitution of powder to prepare a solution for injections

Use aseptic technique throughout entire procedure.

1. Warm the unopened vial containing the solvent (Sterile Water for Injection, EP) to room temperature if necessary, e.g. using a sterile water bath for warming within several minutes (max. +37°C).
2. Remove the protective caps from the FEIBA vial and solvent vial and cleanse the rubber stoppers with germicidal solution of both and allow to dry. 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 gently until all the material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

Fig. a



Fig. b



Fig. c

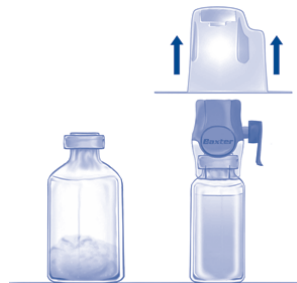


Fig.d



Injection/Infusion

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 plastic injection/infusion devices should be used with FEIBA.

1. Remove the blue cap from BAXJECT II Hi-Flow. Take the syringe and connect it to BAXJECT II Hi-Flow (DO NOT DRAW AIR INTO THE SYRINGE) (Fig. e).
2. Invert the system (with FEIBA vial on top). Draw the FEIBA solution into the syringe by pulling the plunger back slowly (Fig. f).
3. Disconnect the syringe.

4. Slowly inject the solution intravenously with a winged set for injection.

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Fig. e



Fig. f



Do not exceed an infusion rate of 2 U FEIBA/kg/Body Weight per minute.

Do not refrigerate after reconstitution!

After complete reconstitution of FEIBA NF its injection or infusion should be commenced as promptly as practicable, but must be completed within three hours following reconstitution

If you want more information about FEIBA NF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website: shirecanada.com, or by calling 1-800-268-2772.

This leaflet was prepared by Shire Pharma Canada ULC.

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