

# FEIBA NF

## *Factor VIII inhibitor bypassing fraction*

### DESCRIPTION

FEIBA NF is a sterile lyophilized powder containing a complex of coagulation factors. It is intended for intravenous administration after reconstitution.

The potency of FEIBA NF is expressed in arbitrary units. One Unit of activity is defined as that amount of FEIBA NF that shortens the activated partial thromboplastin time (aPTT) of a high titre 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. In addition, 1 - 6 units of Factor VIII coagulation antigen (FVIII C:Ag) per mL are present.

FEIBA NF is prepared from pooled human plasma. During manufacture, the product is subjected to two dedicated viral inactivation steps – vapour heat treatment and nanofiltration.

FEIBA NF is available in two strengths: 50 FEIBA units/mL (2500U and 1000U) and 25 FEIBA units/mL (500U). The composition of the two strengths is given in the following table:

<b>Table 1: FEIBA NF Composition</b>			
	<b>500U (500U/20mL)</b>	<b>1000U (1000U/20mL)</b>	<b>2500U (2500U/50mL)</b>
<b><i>Active ingredient:</i></b>			
Factor VIII inhibitor bypassing fraction As contained in plasma protein	200 - 600mg	400 - 1200mg	1000 – 3000mg
<b><i>Inactive Ingredient:</i></b>			
Sodium Chloride	160mg	160mg	400mg
Sodium Citrate	80mg	80mg	200mg
Sterilised Water for Injection (WFI)	20.0mL	20.0mL	50.0mL

# PHARMACOLOGY

## General

Coagulation involves the activation of factor X to form Xa, which with cofactor Va, catalyses the formation of thrombin from prothrombin. The production of sufficient quantities of Xa usually requires a complex of factors VIIIa and IXa. People (often those with haemophilia A and B) can acquire inhibitors to factor VIII or IX during treatment with factor VIII or IX replacement therapy, which prevent the formation of the complex that catalyses Xa production. FEIBA results in the generation of Xa and thrombin without the help of factor VIIIa-IXa complex, thereby bypassing the inhibitory action of factor VIII (or factor IX) inhibitors.

## CLINICAL TRIALS

Data to support the efficacy and safety of FEIBA NF come from three prospective clinical trials using earlier versions of FEIBA.

The first study<sup>1</sup> was a randomised, double-blind controlled trial comparing an early non-virally inactivated version of FEIBA with a European non-activated prothrombin complex concentrate (Prothrombex). A total of 15 patients with haemophilia A and inhibitors to Factor VIII were enrolled. For each patient, successive bleeds at a particular site were randomised to treatment with one of the two products. A total of 150 bleeds were treated. FEIBA was administered at a dose of 88U/kg (1 – 2 doses) and Prothrombex at a dose of 48IU Factor IX/kg (1 – 2 doses). According to the investigators' assessments, FEIBA was effective or partially effective in 64% of episodes compared to 52% of episodes with Prothrombex.

Data from two other uncontrolled trials<sup>2-3</sup>, in patients with haemophilia A or B with inhibitors, are summarized in the following table.

<b>Study parameters</b>	<b>Hilgartner 1983<sup>(2)</sup></b>	<b>Hilgartner 1990<sup>(3)</sup></b>
<b>FEIBA product used</b>	Non-virally inactivated	Vapour Heat treated
<b>Dose</b>	50U/kg	50 – 75U/kg
<b>Frequency</b>	q 12 hours	q 6-12 hours
<b>Duration of Treatment</b>	3 days	1 – 5 doses
<b>No. of subjects</b>	49	41
<b>No. of bleeds</b>	165	118
<b>% of bleeding episodes controlled</b>	93%	88%

## INDICATIONS

FEIBA NF is indicated for treatment of haemorrhage and to cover surgical interventions in:

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

FEIBA NF 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 (Brackmann *et al.*, 1981).

In addition, FEIBA NF may be used for treating non-haemophiliacs with acquired inhibitors to factors VIII, XI and XII in case of severe or life-threatening haemorrhages.

For guidelines for treatment of patients with F VIII inhibitors see below table.

Inhibitor titre (BU*/mL)	Response to FVIII Treatment	Minor to moderate bleeding	Severe to life-threatening bleeding, surgery
< 5	Low responder	F VIII or FEIBA NF	F VIII or FEIBA NF
< 5	High responder	FEIBA NF	FEIBA NF
5 - 10	Low responder	F VIII or FEIBA NF	FEIBA NF
5 - 10	High responder	FEIBA NF	FEIBA NF
> 10	Low responder	FEIBA NF	FEIBA NF
> 10	High responder	FEIBA NF	FEIBA NF

\* 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.

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

## CONTRAINDICATIONS

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

FEIBA NF is contraindicated in cardiac surgery involving cardiopulmonary bypass and procedures involving extracorporeal membrane oxygenation (ECMO) due to the high risk of thrombotic adverse events.

## PRECAUTIONS

### Thrombotic adverse events

Use of FEIBA NF has been associated with the development of serious thrombotic adverse events such as myocardial infarction, arterial thromboembolism, disseminated intravascular coagulation, deep venous thrombosis and pulmonary embolus. FEIBA NF should be used with caution in subjects with pre-existing risk factors for thrombosis. In all patients, the dose of FEIBA NF should not exceed 100Units per kg per dose or 200Units per kg per day.

### Allergic reactions

FEIBA NF has been associated with severe allergic and anaphylactoid reactions. Patients should be informed of the signs of hypersensitivity reactions such as urticaria, chest tightness, wheezing, hypotension etc. If these symptoms occur, the product should be discontinued immediately. In the case of anaphylactic shock, current medical standards for shock treatment should be implemented.

### Transmission of infectious disease

FEIBA NF is made from human plasma. Products made from human plasma may contain infectious agents that can cause disease, such as viruses and theoretically Creutzfeldt-Jacob Disease (CJD) agents.

Standard measures to prevent infections resulting from the use of plasma-derived products 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 manufacturing process for FEIBA NF includes two such steps (vapor heat treatment and nanofiltration).

Despite this, when plasma-derived products 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 for FEIBA NF are considered effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). They may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients who receive regular/repeated treatment with FEIBA NF.

### **Use in hepatic impairment**

The safety and efficacy of FEIBA NF has not been established in patients with hepatic impairment. Caution should be exercised with such patients.

### **Sodium restriction**

As the quantity of sodium in the maximum daily dose may exceed 200mg, this amount must be taken into consideration for the patients, who are under low sodium restriction.

### **Monitoring of therapy**

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

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 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.

### **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. Thus, attempts to normalise these values by increasing the dose of FEIBA NF may not be successful and are strongly discouraged, because of potential hazard of inducing DIC by overdose.

### **Carcinogenicity**

No carcinogenicity studies have been performed with FEIBA NF.

### **Genotoxicity**

No genotoxicity was observed using a bacterial reversion assay (Ames test).

## Effects on fertility

No fertility studies have been performed with FEIBA NF.

## Use in pregnancy (Category B2)

The effect of FEIBA NF on reproduction and development has not been studied. FEIBA NF should only be given in pregnancy if clearly needed.

## Use in lactation

It is not known whether components from FEIBA NF are excreted in human milk. The safe use of FEIBA NF in lactation has not been established. Caution should be exercised in the administration of FEIBA NF to breastfeeding women.

## Interactions with other drugs

The use of antifibrinolytic agents, such as, epsilon-aminocaproic acid, in combination with FEIBA NF, is not recommended, due to an increased risk of thrombotic events. If treatment with both FEIBA NF and antifibrinolytic agent is indicated, the products should be administered at least 12 hours apart.

# ADVERSE EFFECTS

Serious thrombotic adverse events such as myocardial infarction, arterial thromboembolism, disseminated intravascular coagulation, deep venous thrombosis and pulmonary embolus have been reported (see Precautions).

Hypersensitivity or allergic reactions such as rash, pruritis, urticaria/hives, bronchospasm and facial oedema have been reported (see Precautions).

Other adverse events which have been observed in clinical trials or with post-marketing experience are listed below. In clinical trials, adverse events occurred with a frequency of up to 4% of infusions.

### Body as a whole

- Fever, chills, myalgia.

### Gastrointestinal system

- Nausea, unusual taste in mouth, elevated liver enzymes.

### Central nervous system

- Dizziness, drowsiness, seizure, speech disorder, parasthesiae, anxiety.

Cardiovascular system

- Chest pain/tightness, facial flushing, pulmonary oedema.

## DOSAGE AND ADMINISTRATION

### Dosage

As a general guide a dose of 50 to 100 units of FEIBA NF/kg bodyweight, is recommended. However, total daily dose should not exceed 200U/kg bodyweight.

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

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

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 need not correlate with clinical improvement. For this reason these tests have only a very limited value in monitoring FEIBA NF therapy.

### Dosage: Spontaneous Haemorrhage

#### *Joint, Muscle and Soft Tissue Haemorrhage*

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

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

#### *Mucous Membrane Haemorrhage*

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

#### *Other Severe Haemorrhage*

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

**Dosage: Surgery**

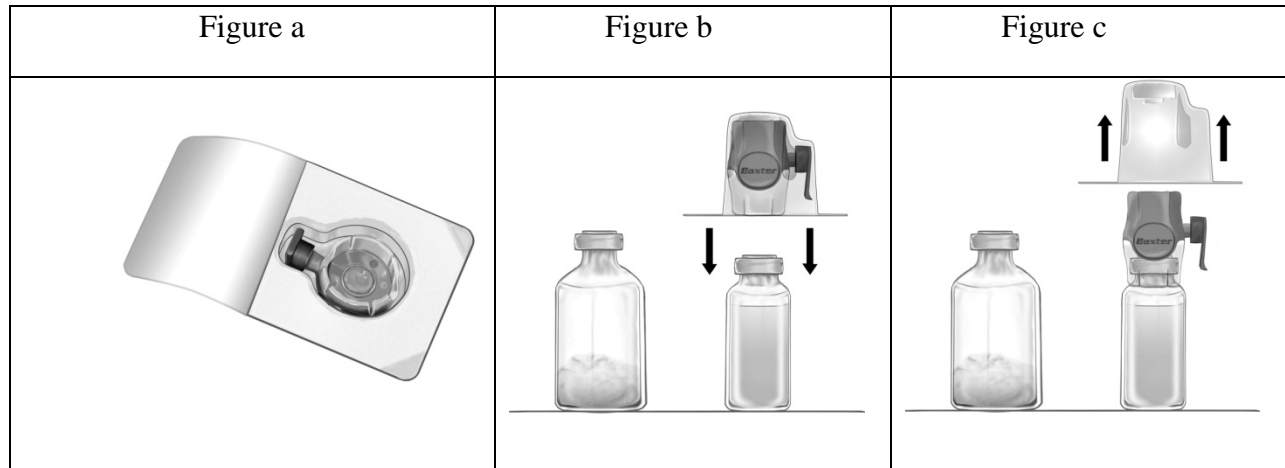
Taking care not to exceed the maximum daily dose, 50 - 100U/kg bodyweight should be given at intervals of up to 6 hours.

**Reconstitution*****General: Use Aseptic Technique***

FEIBA NF is to be reconstituted only immediately before administration. It should then be used promptly, as it does not contain antimicrobial preservatives. Do not refrigerate the reconstituted solution. Do not use solutions which are turbid or have deposits. Any unused solution must be discarded appropriately.

***Reconstitution of powder for injection***

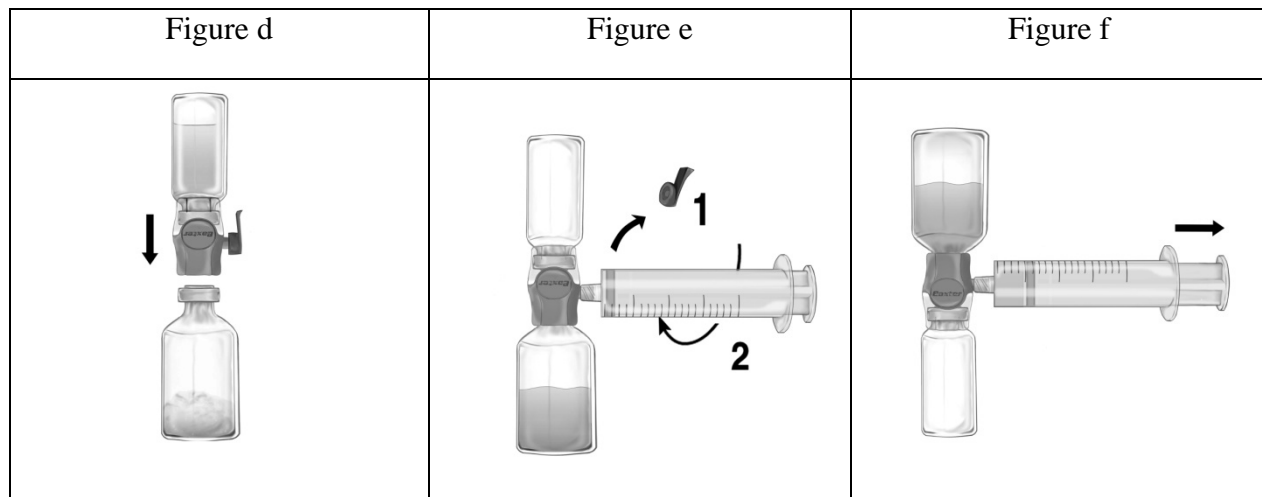
1. Warm solvent (sterilised water for injections) vial to room temperature (15°C – 25°C), for example by using a water bath for several minutes (max. 37°C).
2. Remove the protective caps from the FEIBA NF vial and solvent vial and cleanse the rubber stoppers of both. Place the vials on a flat surface.
3. Open the BAXJECT II Hi-Flow device package by peeling away the paper lid without touching the inside (Fig a). Do not remove the 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 device.
5. With BAXJECT II Hi-Flow attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the purple plastic spike through the FEIBA-NF vial stopper. The vacuum will draw the solvent into the FEIBA-NF vial (Fig. d)
6. Swirl gently until all material is dissolved. Ensure that FEIBA-NF is completely dissolved, otherwise active material will not pass through the device filter.



## Administration

### *Injection/Infusion*

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-NF vial on top). Draw the FEIBA-NF 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 (or a disposable needle)



## Nature and contents of container

Both FEIBA NF powder and the solvent come in vials of surface-treated soda lime glass type II. The product vials are closed with chlorobutyl rubber stoppers, the solvent vials with bromobutyl rubber stoppers.

## OVERDOSAGE

Overdosage of FEIBA NF may increase the risk of adverse effects such as thromboembolism, disseminated intravascular coagulation (DIC) or myocardial infarction. In such cases administration of the product should be stopped promptly and appropriate treatment instituted.

## PRESENTATION AND STORAGE CONDITIONS

FEIBA NF is formulated as a sterile, nonpyrogenic, off-white, lyophilized powder, for intravenous injection. It is supplied in single-dose glass vials.

FEIBA NF 500U packs:

- type II glass vial containing 500 FEIBA-units, lyophilized
- type I glass vial containing 20mL Water for Injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing drugs contained in two vials into a syringe.

FEIBA NF 1000U packs:

- type II glass vial containing 1000 FEIBA-units, lyophilized
- type I glass vial containing 20mL Water for Injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing drugs contained in two vials into a syringe.

FEIBA NF 2500U packs:

- type I glass vial containing 2500 FEIBA-units, lyophilized
- type II glass vial containing 50 mL Water for Injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing drugs contained in two vials into a syringe.

## Shelf Life

Two years. The product is stable for the duration of the specified shelf life when stored in the specified temperature storage condition.

FEIBA-NF should be administered at room temperature not more than 3 hours after reconstitution.

For single use and for one patient only. Discard unused portion of the product.

### **Storage**

Store below 25°C. Do not freeze.

Do not use beyond the expiration date printed on the label.

## **MEDICINE CLASSIFICATION**

General Sale Medicine.

## **NAME AND ADDRESS OF SPONSOR**

### **Manufacturer**

Baxter AG  
Industriestrasse 67  
A-1221-Vienna  
AUSTRIA.

### **Distributor in New Zealand**

Baxter Healthcare Limited  
PO Box 14 062  
Panmure  
Auckland.

### **Distributor in Australia**

Baxter Healthcare Pty Ltd  
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Old Toongabbie, NSW 2146.

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10 May 2011.

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*Please refer to the Medsafe website ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)) for most recent data sheet.*

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## REFERENCES

1. Sjamsoedin L.J.M, Heijnen L, Mauser-Bunschoten E.P. *et al*, “*The Effect of Activated Prothrombin-Complex Concentrate (FEIBA) on joint and muscle bleeding in patients with haemophilia A and antibodies to Factor VIII*”, *New England J. Med.* (1981), **305**, 717-721.
2. Hilgartner M.W, Knatterud G.L., “*FEIBA Study Group, The use of Factor Eight Inhibitor By-Passing Activity (FEIBA Immuno) Product for treatment of bleeding episodes in haemophiliacs with inhibitors*”, *Blood*, (1983), **61**, 36-40.
3. Hilgartner M., Aledort L., Andes A., Gill J., The Members of the FEIBA Study Group: “*Efficacy and safety of vapour-heated anti-inhibitor coagulant complex in haemophilia patients*”, *Transfusion*, (1990), **30**, 626-630.