

AUSTRALIAN PRODUCT INFORMATION

FEIBA NF® (Factor VIII inhibitor bypassing fraction)

1 NAME OF THE MEDICINE

Factor VIII inhibitor bypassing fraction

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Description

FEIBA NF is a sterile lyophilised 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 (2500 U and 1000 U) and 25 FEIBA units/mL (500 U). The composition of the two strengths after reconstitution is given in the following table:

Table 1: FEIBA NF Composition

	500 U	1000 U	2500 U
Active ingredient Factor VIII inhibitor bypassing fraction, As contained in plasma protein	200 – 600 mg	400 – 1200 mg	1000 – 3000 mg

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder and diluent for injection

Appearance

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

FEIBA NF 500 U packs:

- type II glass vial containing 500 FEIBA-units, lyophilised
- type I glass vial containing 20 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.

FEIBA NF 1000 U packs:

- type II glass vial containing 1000 FEIBA-units, lyophilised
- type I glass vial containing 20 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.

FEIBA NF 2500 U packs:

- type I glass vial containing 2500 FEIBA-units, lyophilised
- 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FEIBA NF is indicated for routine prophylaxis, control of spontaneous bleeding episodes and use in surgery in haemophilia A or B patients with inhibitors.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Treatment should be initiated and continued for a period of time under the supervision of a physician experienced in the treatment of coagulation disorders.

Dosage is independent of 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 thromboelastogram (TEG, r-value), and aPTT usually show only a minor shortening and need not correlate with clinical improvement. For these reasons, these tests have only a very limited value in monitoring FEIBA NF therapy. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Table 2 below outlines the dosing recommendations for the administration of FEIBA NF.

Table 2: Dosing Guidelines

	Dose (unit/kg)	Frequency of Doses (hours)	Duration of Therapy
Control and Prevention of Bleeding			
Joint, Muscle and Soft Tissue Haemorrhage	Minor to moderate bleed: 50 - 75	12	Treatment should be continued until clear signs of clinical improvement appear, such as pain, reduction of swelling or mobilization of the joint. A daily dose of 200U/kg body weight should not be exceeded.
	Major muscle and soft tissue haemorrhage (e.g., retroperitoneal bleeding): 100	12	A daily dose of 200U/kg body weight should not be exceeded.
Mucous Membrane Haemorrhage	50 - 100	6	Carefully monitor the patient (visible bleeding site, repeated measurements of haematocrit). If haemorrhage does not stop, the dose may be increased to 100 U/kg body weight. A daily dose of 200U/kg body weight should not be exceeded.
Other Severe Haemorrhage	100	12	Severe haemorrhage, such as CNS bleeding has been effectively treated with doses of 100 U/kg body weight at 12 hours intervals. In individual cases FEIBA NF may be given at intervals of 6 hours until clear clinical improvement is achieved. A daily dose of 200U/kg body weight should not be exceeded.
Surgery	50 - 100	6	A daily dose of 200U/kg body weight should not be exceeded.
Routine Prophylaxis	70 - 100	Every other day	Adjust dose based on the patient's clinical response. A daily dose of 200U/kg body weight should not be exceeded.

Rate of administration

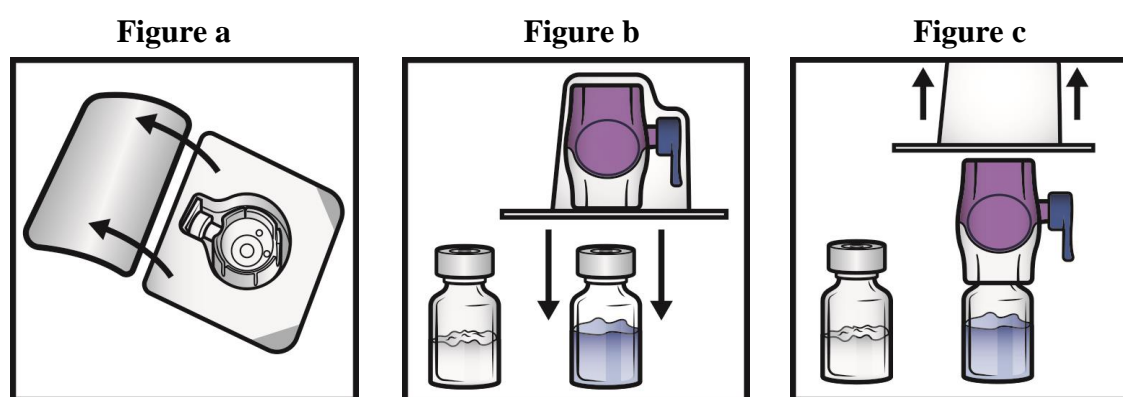
Do not exceed an injection/infusion rate of 2 units FEIBA NF per kg of body weight per minute.

ReconstitutionGeneral: Use Aseptic Technique

FEIBA NF is to be reconstituted immediately before use. It should then be used not more than 3 hours after reconstitution, as it does not contain antimicrobial preservative. Do not refrigerate the reconstituted solution. Do not use solutions, which are turbid or have deposits. Any unused solution must be discarded appropriately.

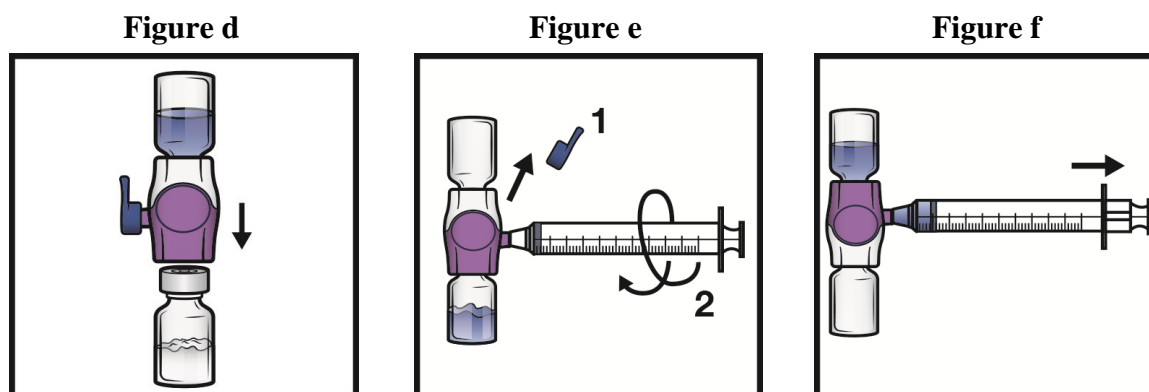
Reconstitution of the powder for injection

1. Warm diluent (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 diluent 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 (Figure a). Do not remove the device from the package.
4. Turn the package over and insert the clear plastic spike through the diluent stopper (Figure b). Grip the package at its edge and pull the package off BAXJECT II Hi-Flow (Figure c). Do not remove the blue cap from BAXJECT II Hi-Flow device.
5. With BAXJECT II Hi-Flow attached to the diluent vial, invert the system so that the diluent vial is on top of the device. Insert the purple plastic spike through the FEIBA NF vial stopper. The vacuum will draw the diluent into the FEIBA NF vial (Figure 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.



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) (Figure 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 (Figure f)
3. Disconnect the syringe.
4. Slowly inject the solution intravenously with a winged set for injection (or a disposable needle)



4.3 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.

FEIBA-NF must not be used in patients with hypersensitivity to the product if therapeutic alternatives to FEIBA NF are available.

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Thromboembolic adverse 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 NF.

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 (rFVIIa) 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 haemophilia.

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 NF 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 (see sections 4.4 and 4.8 in emicizumab Product Information¹; see also Oldenburg et al. *Emicizumab Prophylaxis in Hemophilia A with Inhibitors*. *N Engl J Med* 2017;377:809-818²). The safety and efficacy of FEIBA NF for breakthrough bleeding in patients receiving emicizumab has not been established. Consider the benefits and risks if FEIBA NF must be used in a patient receiving emicizumab prophylaxis. If treatment with FEIBA NF 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.

A single dose of 100 U/kg body weight and a daily dose of 200 U/kg body weight should not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses.

When used to stop bleeding, the product should be given only for as long as absolutely necessary to achieve the therapeutic goal.

Allergic reactions

FEIBA NF can precipitate allergic-type hypersensitivity reactions that have included: urticarial, 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 NF 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 non-allergic), including potential remedial and/or preventative therapy or alternative therapeutic agents.

Viral safety

FEIBA NF is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, such as viruses, the variant Creutzfeldt-Jacob Disease (vCJD) agents and theoretically Creutzfeldt-Jacob Disease (CJD) agent.

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 (vapour 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.

It is recommended that every time FEIBA NF 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.

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

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 500U/1000U contains approximately 80 mg sodium (calculated) per vial
- FEIBA 2500U contains approximately 200 mg sodium (calculated) per vial

Monitoring of therapy and clinical efficacy

Single doses of 100 Units/kg body weight and daily doses of 200 Units/kg body weight should not be exceeded. Patients given single doses of 100 Units/kg body weight should be monitored for the development of DIC, acute coronary ischemia, and signs and symptoms of other thrombotic or thromboembolic events. High doses of FEIBA NF should be given only for as long as 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 product (FDP). Other indications of DIC include significantly prolonged thrombin time, prothrombin time, or partial thromboplastin time.

Due to patient-specific factors, the response to a bypassing agent can vary and, in a specific 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.

In vitro tests to control efficacy such as aPPT, whole blood clotting time (WBCT), and thromboelastogram (TEG) may not correlate with clinical improvement. Thus, attempts to normalize 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.

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.

Administration of FEIBA NF to patients with inhibitors may result in an initial “anamnestic” rise in inhibitor levels. Upon continued administration of FEIBA NF, inhibitors may decrease over time.

Use in the elderly

No data available.

Paediatric use

The experience in children under 6 years of age is limited. The same dose regimen as in adults should be adapted to the child’s clinical condition.

Effects on laboratory tests

FEIBA NF 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).

After administration of high doses of FEIBA NF, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

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 NF was used as part of a treatment regimen for breakthrough bleeding (see sections 4.4, 4.5 and 4.8 in emicizumab Product Information⁴)

There is a theoretical risk that active immunity from a live attenuated vaccine may not develop because of interference from circulating antibodies to the vaccine virus. Antibodies from any source (e.g., transplacental, transfusion) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure). Whether this type of interference can occur with the levels of antibodies present in the passive transfer associated with the use of FEIBA is not known. If the response to the vaccine is altered, additional testing and/or re-vaccination may be required.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been performed with FEIBA NF.

Use in pregnancy

Australian Pregnancy Categorisation (Category B2)

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

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

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions from clinical trials

The adverse reactions presented in the table were reported in the original FEIBA studies (Hilgartner 1983, 2003; Sjamsoedin LJ. *et al.*,1981) for the treatment of bleeding episodes in haemophilia A or B patients with inhibitors to Factors VIII or IX and the randomised, prospective prophylaxis study (090701) comparing prophylaxis with on-demand treatment.

Table 3: 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 titre (anamnesic response)*, a	Unknown	–
IMMUNE SYSTEM DISORDERS	Hypersensitivity ^c	Common	1/36 (2.8)
NERVOUS SYSTEM DISORDERS	Somnolence*	Unknown	–
	Dizziness ^b	Common	1/36 (2.8)
	Dysgeusia*	Unknown	–
	Headache ^c	Common	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*	Unknown	–
	Pyrexia*	Unknown	–
	Chest pain*	Unknown	–
	Chest discomfort*	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; Sjamsoedin LJ. et al., 1981) only.
- ^a Increase of inhibitor titre (anamnesic response) [not a MedDRA PT] is the rise of previously existing inhibitor titer occurring after the administration of FEIBA. See Section 4.4.
- ^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.

Post-Marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA (version 18.0) System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Disseminated intravascular coagulation

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction

NERVOUS SYSTEM DISORDERS: Paraesthesia, 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, Diarrhoea, Abdominal discomfort

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema, Urticaria, Pruritus

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

Class Reactions

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

Other Adverse Reactions

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: myalgia

GASTROINTESTINAL SYSTEM: elevated liver enzymes

CENTRAL NERVOUS SYSTEM: seizure, speech disorder, anxiety

CARDIOVASCULAR SYSTEM: pulmonary oedema.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

Some reported thromboembolic events have occurred with doses above 200 U/kg. In such cases administration of the product should be stopped promptly and appropriate treatment instituted.

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 the treatment with Factor VIII or IX replacement therapy, which prevent the formation of the complex that catalyses Xa production. FEIBA NF 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 bleeding sites were joint 117, muscle 29 and mucocutaneous 4.

The first study³ was a randomised, double-blind controlled trial comparing an early non-virally inactivated version of FEIBA with a European non-activated prothrombin complex concentrate (PROTHROMBLEX). The median age of patients was 12 years, range 3-37 years. In Hilgartner 1983, three patients had haemophilia B with inhibitors and two patients had acquired Factor VIII inhibitors. Patients were aged greater than 4 years. 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 88 U/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, in patients with haemophilia A or B with inhibitors, are summarised in the following table.

Table 4: Results of Uncontrolled Clinical Trials

Study parameters	Hilgartner 1983⁽⁴⁾	Hilgartner 1990⁽⁵⁾
FEIBA product used	Non-virally inactivated	Vapour Heat treated
Dose	50 U / kg	50 – 75 U / kg
Frequency	q 12 hours	q 6-12 hours
Duration of Treatment	3 days	1 – 5 doses
No of subjects	49	41
No of bleeds	165	106*
% of bleeding episodes controlled	93%	88%

* evaluable

In Hilgartner 1983, the bleeding sites were joint 102, muscle/soft tissue 33, mucus membrane 20, surgical 4, central nervous system 3, nose 1, chest wall 1 and auditory canal 1. In Hilgartner 1990, the bleeding sites were joint 73, muscle/soft tissue 16, mucous membrane 9, surgical 7, central nervous system 1 and excluded due to protocol violation 12. The majority of patients had haemophilia A with inhibitors: 44 in Hilgartner 1983 and all patients in Hilgartner 1990.

The use of FEIBA prophylaxis was assessed in a global multicentre trial in haemophilia A or B subjects with high titre or low titre inhibitors refractory to FVIII or FIX treatment. The trial was a randomised, open-label, parallel-group study comparing prophylactic versus on-demand treatment with FEIBA. Subjects randomised to prophylaxis received 70-100 U/kg every other day. If a bleeding episode occurred, FEIBA was dosed at the discretion of the treating doctor in both treatments groups based on the protocol dosing guidance. The duration of the study was 12 months.

Thirty six subjects entered the study, 17 randomised to prophylaxis and 19 to on-demand. All were included in the intent-to-treat analysis. The two groups were similar in baseline demographic and disease characteristics. All subjects were male. The median age was 23.5 years, range 7-56 years.

The primary endpoint was reduction in annualised bleeding rate (ABR) in the prophylaxis arm compared to the on-demand arm. Prophylaxis with FEIBA significantly reduced the annualised bleeding rate (see Table 5). The results were also confirmed in a negative binomial mixed effects model. Most (79%) of the bleeds were treated with 1-2 infusions of FEIBA. Haemostatic efficacy was rated as excellent or good in 87% of bleeding episodes at 24 hours in both arms. The majority of bleeds in both groups involved the joints. Administration of FEIBA prophylactically significantly reduced both joint and non-joint bleeds as well as spontaneous and traumatic bleeds.

Prophylaxis with FEIBA also significantly increased the time between bleeds overall by a median of 9 days (Table 5). In the case of time between joint bleeds, the trend was in favour of prophylaxis.

**Table 5: Results of FEIBA Prophylaxis Clinical Trial (090701)
Efficacy Intent-to-Treat Analysis Set**

Variable	Prophylaxis (n=17)	On-Demand (n=19)	Difference p-value
No. of patients with bleeding episodes (%)	14 (82%)	19 (100%)	
No. Of Bleeding Episodes			
All	196	629	
Joint	171	572	
Non-Joint	25	57	
ABR median			
All	7.9	28.7	P=0.0003 ¹
Joint	6.0	22.9	P=0.0006 ¹
Non-Joint	0.5	2.9	P=0.0227 ¹
Spontaneous	5.6	18.9	P=0.0008 ¹
Traumatic	2.5	4.7	P=0.0199 ¹
Time between bleeds			
Days median			
All	20.0	11.0	P=0.0097 ²
Joint	20.0	12.0	
Non-Joint	Not stated	Not stated	

¹ 2-sided two-sample t-test of mean transformed annualised bleeding rate. The data was transformed to a normal distribution using $X' = \text{SQRT}(X+0.5)$ where $X = \text{bleeds/year}$.

² 2-sided Mann-Whitney test (Wilcoxon Rank Sum) for the difference in medians.

5.2 PHARMACOKINETIC PROPERTIES

Not available

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

No carcinogenicity studies have been performed with FEIBA NF.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Table 6: FEIBA NF Inactive ingredients

	500 U	1000 U	2500 U
Inactive ingredient:			
Sodium Chloride	160 mg	160 mg	400 mg
Sodium Citrate	80 mg	80 mg	200 mg
Diluent:			
Water for Injections	20.0 mL	20.0mL	50.0 mL

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The shelf life of FEIBA NF is 2 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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

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

6.5 NATURE AND CONTENTS OF CONTAINER

FEIBA NF powder and diluent are supplied in vials (powder vial for 2500 U: hydrolytic type I borosilicate glass; powder vial for 500 U and 1000 U: hydrolytic type II surface treated soda lime glass; diluent vial for 50 ml: hydrolytic type II surface treated soda lime glass; diluent vial for 20 ml hydrolytic Type I surface treated soda lime glass) closed with butyl rubber stoppers and protective caps.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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.

CAS number

Not available

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled.

8 SPONSOR

Shire Australia Pty Limited
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.shireaustralia.com.au

9 DATE OF FIRST APPROVAL

500 U: 09 January 2007.

1000 U: 09 January 2007.

2500 U: 30 March 2012.

10 DATE OF REVISION

3 August 2018

Summary table of changes

Section Changed	Summary of new information
All	Australian PI updated to new SPC format
4.2, 4.4, 4.8, 5.1, 6.1, 6.5, 8	Minor editorial changes including typographical changes
4.2	Images updated due to sponsor change
4.3	Safety update: added contraindications in patients with hypersensitivity if therapeutic alternatives are available
4.4	Safety update: addition of isohemagglutinins precaution and addition of TMA warning; new safety text
4.5	Safety update: addition of a potential drug interaction; new safety text added.
4.6	Safety update: additional considerations added
8	Change in sponsor contact details

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