

NEW ZEALAND DATA SHEET

1 FEIBA NF (500 U, 1000 U and 2500 U injection with diluent)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Factor VIII inhibitor bypassing fraction 500 U, 1000 U and 2500 U.

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 (FVIII) inhibitor reference plasma to 50% of the blank value.

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:

<i>FEIBA NF Composition</i>			
<i>Active ingredient:</i>			
Factor VIII inhibitor bypassing fraction	500 U (500 U/20 mL)	1000 U (1000 U/20 mL)	2500 U (2500 U/50 mL)
As contained in plasma protein	200 – 600 mg	400 – 1200 mg	1000 – 3000 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injection with diluent.

FEIBA NF is a sterile lyophilised powder containing a complex of coagulation Factors.

FEIBA NF is formulated as a sterile, nonpyrogenic, off-white, lyophilised powder, for intravenous injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

On-demand and surgery indication

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

- Haemophilia A patients with FVIII inhibitor
- Haemophilia B patients with FIX 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 FVIII inhibitor so as to allow for regular treatment with FVIII concentrate as in patients without inhibitor.

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.

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For guidelines for treatment of patients with FVIII inhibitors see following table.

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

Prophylactic indication

FEIBA NF is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in haemophilia A subjects with inhibitors experiencing ≥ 12 bleeding episodes per year. Prophylaxis with **FEIBA NF** is recommended for patients with high titre (> 5 BU) inhibitor or low titre (< 5 BU) inhibitor, refractory to increased dosing with FVIII or FIX.

4.2 Dose and method of administration

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

FEIBA NF is intended for intravenous administration after reconstitution.

Dose

As a general rule a dose of 50 to 100 units of **FEIBA NF**/kg (U/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 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 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. The following table outlines the dosing recommendations for the administration of **FEIBA NF**.

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<i>Dosing Guidelines</i>			
	<i>Dose (unit/kg)</i>	<i>Frequency of Doses (hours)</i>	<i>Duration of Therapy</i>
<i>Control and Prevention of Bleeding</i>			
<i>Joint, Muscle and Soft Tissue Haemorrhage</i>	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 200 U/kg body weight should not be exceeded.
	Major muscle and soft tissue haemorrhage (e.g., retro-peritoneal bleeding): 100	12	A daily dose of 200 U/kg body weight should not be exceeded.
<i>Mucous Membrane Haemorrhage</i>	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 200 U/kg body weight should not be exceeded.
<i>Other Severe Haemorrhage</i>	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 200 U/kg body weight should not be exceeded.
<i>Surgery</i>	50 - 100	6	A daily dose of 200 U/kg body weight should not be exceeded.
<i>Routine Prophylaxis</i>	70 - 100	Every other day	Adjust dose based on the patient's clinical response. A daily dose of 200 U/kg body weight should not be exceeded.

Use in children

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.

Rate of administration

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

Reconstitution

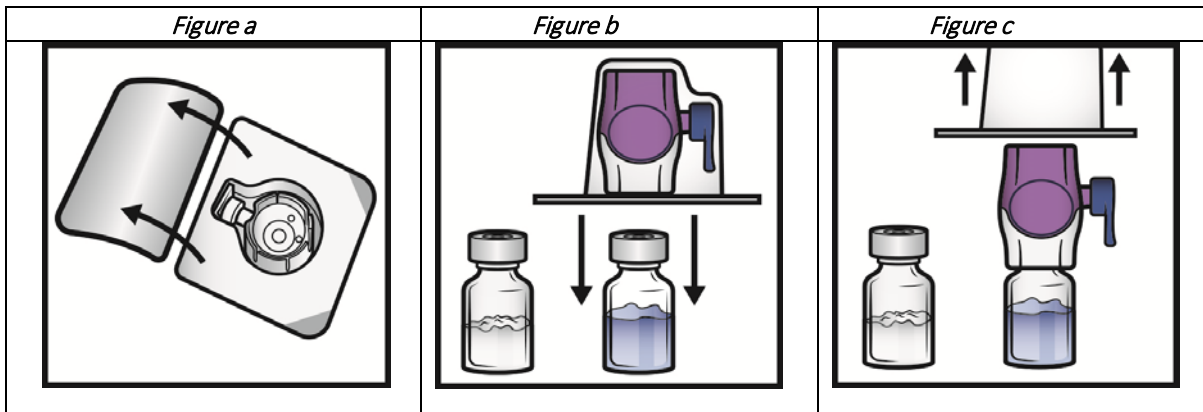
General: Use aseptic technique.

FEIBA NF is to be reconstituted only immediately before use. It should then be used not more than 3 hours after reconstitution, 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.

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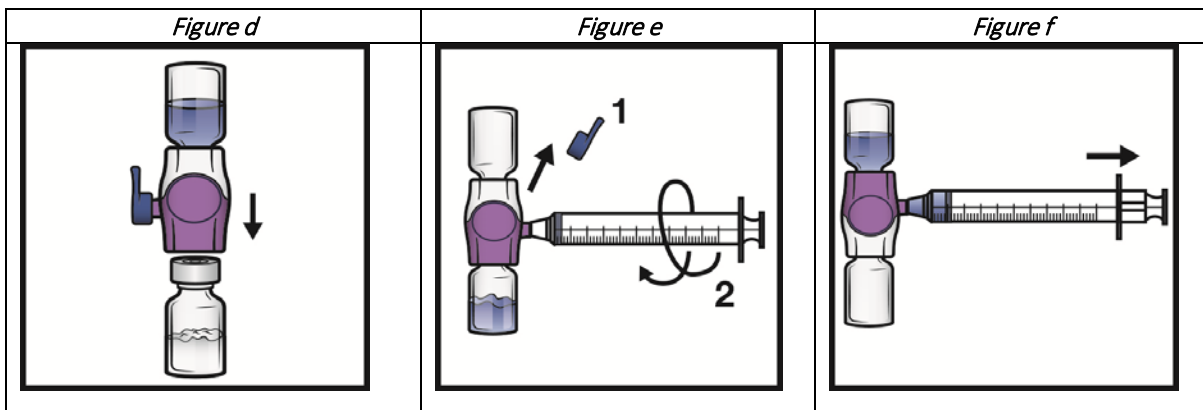
Reconstitution of powder for injection

1. Warm diluent (water for injection) 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).



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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.

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 septicaemia) 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 NF should be used with particular caution in patients at risk of DIC 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, 4.5 and 4.8 of emicizumab Data Sheet¹; 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.

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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 NF** 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 (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**.

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.

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

Monitoring of therapy and clinical efficacy

Single doses of 100 U/kg body weight and daily doses of 200 U/kg body weight should not be exceeded. Patients given single doses of 100 U/kg body weight should be monitored for the development of DIC, acute coronary ischaemia, 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 products (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 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.

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. Clinical and published data suggest that the efficacy of **FEIBA NF** is not reduced.

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 Interaction with other medicines and other forms of interaction

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

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with both **FEIBA NF** and 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 rFVIIa, 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.¹

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., trans-placental, 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 (Category B2)

Medicines 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.

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4.8 Undesirable effects

Adverse reactions from clinical trials

The adverse reactions presented in the table were reported in the original FEIBA studies (Hilgartner 1983, 1990; 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 (O90701) comparing prophylaxis with on-demand treatment.

<i>Adverse Reactions from Clinical Trials</i>			
<i>System Organ Class (SOC)</i>	<i>Preferred MedDRA (version 18.0) Term</i>	<i>Frequency Category</i>	<i>Frequency Ratio (Percentage) n = 36</i>
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Increase of inhibitor titre (anamnestic 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	Dyspnoea*	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 (8.38)

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, 1990; Sjamsoedin LJ. *et al.*, 1981) only.

a Increase of inhibitor titre (anamnestic response) [not a MedDRA PT] is the rise of previously existing inhibitor titres occurring after the administration of FEIBA. See section 4.4.

b ADR reported in the original studies (Hilgartner 1983, 1990; Sjamsoedin LJ. *et al.*, 1981) and prophylaxis study (O90701). Frequency shown is from the prophylaxis study.

c ADR reported in the prophylaxis study (O90701). 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

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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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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 advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Activated Prothrombin Complex against FVIII Antibodies.

ATC Code

B02BD03.

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

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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.

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.

5.2 Pharmacokinetic properties

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 (Prothrombex). 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 48 U 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.

<i>Results of Uncontrolled Clinical trials</i>		
<i>Study parameters</i>	<i>Hilgartner 1983⁴</i>	<i>Hilgartner 1990⁵</i>
<i>FEIBA product used</i>	Non-virally inactivated	Vapour Heat treated
<i>Dose</i>	50U/kg	50 – 75U/kg
<i>Frequency</i>	q 12 hours	q 6 – 12 hours
<i>Duration of Treatment</i>	3 days	1 – 5 doses
<i>No. of subjects</i>	49	41
<i>No. of bleeds</i>	165	106*
<i>% of bleeding episodes controlled</i>	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.

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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 following table). 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 (see following table). In the case of time between joint bleeds, the trend was in favour of prophylaxis.

<i>Results of FEIBA Prophylaxis Clinical Trial (090701)</i>			
<i>Efficacy Intent-to-Treat Analysis Set</i>			
<i>Variable</i>	<i>Prophylaxis (n = 17)</i>	<i>On-Demand (n = 19)</i>	<i>Difference p-value</i>
<i>No. of patients with bleeding episodes (%)</i>	14 (82%)	19 (100%)	
<i>No. of Bleeding Episodes</i>			
All	196	629	
Joint	171	572	
Non-Joint	25	57	
<i>ABR median</i>			
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
<i>Time between bleeds, Days median</i>			
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 = bleeds/year.			
² 2-sided Mann-Whitney test (Wilcoxon Rank Sum) for the difference in medians.			

5.3 Preclinical safety data

Carcinogenicity

No carcinogenicity studies have been performed with FEIBA NF.

Genotoxicity

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

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium citrate dihydrate

Water for injections (diluent)

6.2 Incompatibilities

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or solvents.

Only the provided infusion sets should be used.

It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of **FEIBA NF**.

6.3 Shelf life

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.

6.4 Special precautions for storage

Store below 25°C. Protect from light. 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 single-dose glass vials, closed by butyl rubber stoppers and protective caps.

The powder is supplied in hydrolytic type I or type II glass vials. Type I glass vials are used for filling the powder for 2500 U/50 mL; and type II glass vials are used for filling the powder for 500 U/20 mL and 1000 U/20 mL.

The diluent is supplied in hydrolytic type I glass vials containing 20 mL or 50 mL water for injections.

Each **FEIBA NF** 500U pack contains:

- 1 powder vial of 500 FEIBA-units
- 1 diluent vial of 20 mL water for injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing medicines contained in two vials into a syringe.

NEW ZEALAND DATA SHEET

Each FEIBA NF 1000U pack contains:

- 1 powder vial of 1000 FEIBA-units
- 1 diluent vial of 20 mL water for injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing medicines contained in two vials into a syringe.

Each FEIBA NF 2500U pack contains:

- 1 powder vial of 2500 FEIBA-units
- 1 diluent vial of 50 mL water for injections
- 1 BAXJECT II Hi-Flow– Needleless transfer device intended for transferring and mixing medicines contained in two vials into a syringe.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

FEIBA NF is distributed in New Zealand by:

Shire New Zealand Ltd
(now part of Takeda)
C/o Crowe Horwath
Level 29, 188 Quay Street
Auckland Central
Auckland 1010

Telephone: 0508 169 077.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

FEIBA NF 500U and 1000U 27 November 2003

FEIBA NF 2500U 26 May 2011.

10 DATE OF REVISION OF THE TEXT

07 June 2019

SUMMARY TABLE OF CHANGES

<i>Section changed</i>	<i>Summary of new information</i>
6.1	Correction of excipient name
6.4	Additional approved storage condition added
6.5	Changed container material for the 50 mL diluent vial for 2500 U
1, 2, 4.2, 4.4, 4.8, 4.9, 5.2, 8	Minor editorial and/or formatting changes including typographical corrections.

NEW ZEALAND DATA SHEET

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

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REFERENCES

¹ New Zealand approved Data Sheet for emicizumab

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³ 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.

⁴ 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.

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