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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Factor VIII inhibitor bypassing fraction 500IU, 1000IU and 2500IU.

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 after reconstitution is given in the following table:

<table>
<thead>
<tr>
<th>FEIBA NF Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient:</td>
</tr>
<tr>
<td>Factor VIII inhibitor bypassing fraction As contained in plasma protein</td>
</tr>
<tr>
<td>200 - 600mg</td>
</tr>
</tbody>
</table>

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Injection with diluent.

FEIBA NF is a sterile lyophilized powder containing a complex of coagulation factors.

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 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.

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 following table.
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.

**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 titer (> 5 BU) inhibitor or low titer (< 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 body weight, is recommended. However, total daily dose should not exceed 200U/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**.

<table>
<thead>
<tr>
<th>Inhibitor titre (BU*/mL)</th>
<th>Response to FVIII Treatment</th>
<th>Minor to moderate bleeding</th>
<th>Severe to life-threatening bleeding, surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>Low responder</td>
<td>F VIII or FEIBA NF</td>
<td>F VIII or FEIBA NF</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>High responder</td>
<td>FEIBA NF</td>
<td>FEIBA NF</td>
</tr>
<tr>
<td>5 – 10</td>
<td>Low responder</td>
<td>F VIII or FEIBA NF</td>
<td>FEIBA NF</td>
</tr>
<tr>
<td>5 – 10</td>
<td>High responder</td>
<td>FEIBA NF</td>
<td>FEIBA NF</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Low responder</td>
<td>FEIBA NF</td>
<td>FEIBA NF</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>High responder</td>
<td>FEIBA NF</td>
<td>FEIBA NF</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Dose (unit/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control and Prevention of Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Joint, Muscle and Soft Tissue Haemorrhage</strong></td>
<td>Minor to moderate bleed: 50 - 75</td>
<td>12</td>
</tr>
</tbody>
</table>
### 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 units **FEIBA NF** per 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.

### 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.

**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).

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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.
**NEW ZEALAND DATA SHEET**

**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.

### 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 200U/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 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.

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 100U/kg body weight and a daily dose of 200U/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** 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.

**Viral safety**

**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 body weight and daily doses of 200units/kg body weight should not be exceeded. Patients given single doses of 100units/kg body weight 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 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.

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 overdosage.

Interaction with other medicines and other forms of interaction
The use of antifibrinolytic agents, such as, epsilon-aminoacaproic acid, in combination with FEIBA NF, is not recommended, due to an increased risk of thromboembolic events. If treatment 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 recombinant Factor VIIa or antifibrinolytics 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).

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.

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
No effects on the ability to drive and use machines have been observed.

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, 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 randomized, prospective prophylaxis study (090701) comparing prophylaxis with on-demand treatment.

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred MedDRA (version 17.0) Term</th>
<th>Frequency Category</th>
<th>Frequency Ratio (Percentage) n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD AND LYMPHATIC SYSTEM DISORDERS</td>
<td>Increase of inhibitor titer (anamnestic response)*, a</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>IMMUNE SYSTEM DISORDERS</td>
<td>Hypersensitivity*</td>
<td>Common</td>
<td>1/36 (2.8)</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>Somnolence*</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Common</td>
<td>1/36 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia*</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache*</td>
<td>Common</td>
<td>1/36 (2.8)</td>
</tr>
<tr>
<td>VASCULAR DISORDERS</td>
<td>Hypotension*</td>
<td>Common</td>
<td>1/36 (2.8)</td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS</td>
<td>Dyspnoea*</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td>Nausea*</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS</td>
<td>Rash*</td>
<td>Common</td>
<td>1/36 (2.8)</td>
</tr>
</tbody>
</table>
### Clinical Trial Adverse Reactions

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred MedDRA (version 17.0) Term</th>
<th>Frequency Category</th>
<th>Frequency Ratio (Percentage) n = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td>Chills*</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Pyrexia*</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Chest pain*</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Chest discomfort*</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td><strong>INVESTIGATIONS</strong></td>
<td>Hepatitis B surface antibody positive(^c)</td>
<td>Common</td>
<td>3/36 (8.38)</td>
</tr>
</tbody>
</table>

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 < 1/10), Uncommon (≥1/1,000 < 1/100), Rare (≥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 titer (anamnestic response) (not a MedDRA PT) is the rise of previously existing inhibitor titers 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.

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**Post-marketing adverse reactions**

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA (version 15.1) 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 reactions 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.
NEW ZEALAND DATA SHEET

BODY AS A WHOLE: Myalgia.

GASTROINTESTINAL SYSTEM: Elevated liver enzymes.

CENTRAL NERVOUS SYSTEM: Seizure, speech disorder, anxiety.

CARDIOVASCULAR SYSTEM: Pulmonary oedema.

4.9 Overdose
Some reported thromboembolic events have occurred with doses above 200U/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 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.

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 study 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 88U/kg (1 – 2 doses) and Prothromblex 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 Prothromblex.

Data from two other uncontrolled trials, in patients with haemophilia A or B with inhibitors, are summarized in the following table.
NEW ZEALAND DATA SHEET

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

* 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, mucus 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 NF prophylaxis was assessed in a global multicentre trial in haemophilia A or B subjects with high titer or low titer 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 NF. Subjects randomised to prophylaxis received 70 - 100U/kg every other day. If a bleeding episode occurred, FEIBA NF 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 NF 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 NF. 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 NF prophylactically significantly reduced both joint and non-joint bleeds as well as spontaneous and traumatic bleeds.

Prophylaxis with FEIBA NF 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.
Results of FEIBA Prophylaxis Clinical Trial (090701)
Efficacy Intent-to-Treat Analysis Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prophylaxis (n = 17)</th>
<th>On-Demand (n = 19)</th>
<th>Difference p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with bleeding episodes (%)</td>
<td>14 (82%)</td>
<td>19 (100%)</td>
<td></td>
</tr>
<tr>
<td>No. Of Bleeding Episodes</td>
<td>196</td>
<td>629</td>
<td>283</td>
</tr>
<tr>
<td>Joint</td>
<td>171</td>
<td>572</td>
<td>395</td>
</tr>
<tr>
<td>Non-Joint</td>
<td>25</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>ABR median</td>
<td>7.9</td>
<td>28.7</td>
<td>20.8</td>
</tr>
<tr>
<td>All</td>
<td>6.0</td>
<td>22.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Joint</td>
<td>0.5</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-Joint</td>
<td>5.6</td>
<td>18.9</td>
<td>13.3</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>2.5</td>
<td>4.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Traumatic</td>
<td>2.5</td>
<td>4.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Time between bleeds, Days median</td>
<td>20.0</td>
<td>11.0</td>
<td>9.0</td>
</tr>
<tr>
<td>All</td>
<td>20.0</td>
<td>12.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Joint</td>
<td>20.0</td>
<td>12.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Non-Joint</td>
<td>Not stated</td>
<td>Not stated</td>
<td></td>
</tr>
</tbody>
</table>

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.

5.3 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<table>
<thead>
<tr>
<th>FEIBA NF Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredients:</td>
</tr>
<tr>
<td>Sodium Chloride</td>
</tr>
<tr>
<td>Sodium Citrate</td>
</tr>
<tr>
<td>Sterilised Water for Injection (WFI)</td>
</tr>
</tbody>
</table>

6.2 Incompatibilities

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.
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.

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 is formulated as a sterile, nonpyrogenic, off-white, lyophilized powder, for intravenous injection.

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

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 medicines 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 medicines 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 50mL 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.
NEW ZEALAND DATA SHEET

8 SPONSOR

FEIBA NF is distributed in New Zealand by:

Shire New Zealand Ltd
C/o Crowe Horwath
PO Box 158
Shortland Street
Auckland 1010

Shire New Zealand Ltd
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 500IU and 1000IU 27 November 2003
FEIBA NF 2500IU 26 May 2011.

10 DATE OF REVISION OF THE TEXT

18 October 2017.

SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Sponsor details and contact telephone number updated.</td>
</tr>
<tr>
<td>10</td>
<td>Date of Revision of Text updated.</td>
</tr>
<tr>
<td>Footer</td>
<td>Footer date and company name updated.</td>
</tr>
</tbody>
</table>

Based on Australian PI approved 13 December 2006; most recent amendment 9 October 2015; and CCSI 209 2013 0103.

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

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