SUMMARY OF PRODUCT CHARACTERISTICS

FEIBA NF

Factor VIII Inhibitor Bypassing Activity

Powder for Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

FEIBA NF (Factor VIII Inhibitor Bypassing Activity)

Powder and solvent for the production of a solution for intravenous administration.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(a) Powder: each glass vial contains:

FEIBA NF	**500 U***	**1000 U***
Active ingredient:		
Human Plasma Protein with a Factor Eight Inhibitor Bypassing Activity of	200-600 mg 500 units	400-1200 mg 1000 units
Other ingredients:		
Sodium Chloride	160 mg	160 mg
Sodium Citrate dihydrate	80 mg	80 mg

*) A solution containing 1 U of FEIBA NF shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma to 50% of the buffer value (blank).

FEIBA NF also contains factors II, IX and X mainly in non-activated form as well as activated factor VII; factor VIII coagulant antigen (F VIII C:Ag) is present in a concentration of up to 0.1 U/1 U FEIBA NF. The factors of the kallikrein-kinin system are present only in trace amounts, if at all.

(b) Solvent: each glass vial contains 20 ml sterile water for injections.

3. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection.

White, off-white or pale green freeze-dried powder or friable solid. The pH value of the reconstituted solution is between 6.8 and 7.6.

FEIBA NF is available in strengths of 500 U and 1000 U, to be dissolved in 20 ml of sterilised water for injections.

The reconstituted product is intended for intravenous administration.

4. CLINICAL PARTICULARS

4.1 Therapeutical Indications

- Control of bleeding episodes in haemophilia A patients with Factor VIII inhibitors and also in patients with acquired Factor VIII inhibitors.

- Control of bleeding in hemophilia B patients with inhibitors, if no other specific treatment is available.

4.2. Posology and Method of Administration

The treatment should be initiated and supervised by a physician experienced in the management of coagulation disorders.

Posology

Dosage and duration of the therapy depend on the severity of the haemostasis disorders, the localization and the extent of the bleeding, as well as the clinical condition of the patient.

Dosage and frequency of administration should always be guided by the clinical efficacy in the individual case.

As a general guideline a dose of 50 to 100 U of FEIBA NF per kg body weight (bw) is recommended; a single dose of 100 U/kg body weight and a maximum daily dose of 200 U/kg body weight must not be exceeded unless the severity of bleeding warrants and justifies the use of higher doses. See Section 4.4.

Paediatric use (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.

1) Spontaneous Bleeding
Joint, Muscle and Soft Tissue Haemorrhage
A dose of 50-75 U/kg body weight at 12-hour intervals is recommended for minor to moderately severe bleeding The treatment should be continued until a clear improvement of the clinical symptoms, e.g. reduction relief of pain, decrease of swelling or increase of joint mobility occurs.

For severe muscle and soft tissue bleeding, e.g. retroperitoneal hemorrhages, a dose of 100 U/kg body weight at 12-hour intervals is recommended.

Mucous Membrane Haemorrhage
A dose of 50 U/kg body weight every 6 hours under careful monitoring of the patient (visual control of bleeding, repeated determination of hematocrit) is recommended. If the bleeding does not stop, the dose may be increased to 100 U/kg body weight, however a daily dose of 200 U/kg body weight must not be exceeded.

Other Severe Haemorrhages
In severe hemorrhage, such as CNS bleeding, a dose of 100 U/kg body weight at 12-hour intervals is recommended. In individual cases, FEIBA NF may be administered at 6-hour intervals, until clear improvement of the clinical condition is achieved. (The maximum daily dose of 200 U/kg body weight must not be exceeded!)

2) Surgery
In surgical interventions, an initial dose of 100 U/kg body weight may be administered preoperatively, and a further dose of 50 – 100 U/kg body weight may be administered after 6 – 12 hours. As a postoperative maintenance dose, 50 – 100 U/kg body weight may be administered at 6 – 12-hour intervals; dosage, dosage intervals and duration of the peri- and postoperative therapy are guided by the surgical intervention, the patient's general condition and the clinical efficacy in each individual case. (The maximum daily dose of 200 U/kg body weight must not be exceeded!)

3) Use of FEIBA NF in special patient groups

See Section 5.1 for information in relation to hemophilia B patients with factor IX inhibitor.

In combination with factor VIII concentrate, FEIBA NF was also used for long term therapy to achieve complete and permanent elimination of the factor VIII inhibitor.

Monitoring
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 is considered to be necessary for the efficacy of the product.

Due to the complex mechanism of action, no direct monitoring of active ingredients is available. Coagulation tests such as the whole blood coagulation time (WBCT), the thromboelastogram (TEG, r-value) and the aPTT usually show only little reduction and do not necessarily correlate with the clinical efficacy. Therefore these tests have little significance in the monitoring of the therapy with FEIBA NF. See Section 4.4.

Method of Administration

Reconstitute the product as described in Section 6.6 RECONSTITUTION OF THE POWDER FOR SOLUTION FOR INJECTION WITH THE BAXJECT II HI-FLOW OR RECONSTITUTION OF THE POWDER FOR SOLUTION FOR INJECTION WITH TRANSFER NEEDLE, and inject or infuse slowly by the intravenous route only. Do not exceed an injection/infusion rate of 2 U/kg bw per minute.

4.3 CONTRAINDICATIONS

FEIBA NF must not be used in the following situations if therapeutic alternatives to FEIBA NF are available:

- Hypersensitivity to the product or any of the components.
- Disseminated Intravascular Coagulation (DIC).
- Acute thrombosis or embolism (including myocardial infarction).

See Section 4.4.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

WARNINGS

Hypersensitivity Reactions

FEIBA NF can precipitate allergic-type hypersensitivity reactions that have included, urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension; these reactions can be severe and can be systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported.
Patients should be informed of the early signs of hypersensitivity reactions, for example erythema, skin rash, generalized urticaria, pruritus, breathing difficulties/dyspnoea, tightness of the chest, general indisposition, dizziness and drop in blood pressure up to allergic shock.
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 suspected hypersensitivity to the product or any of its components, 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.

Thromboembolic 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 may increase the risk of developing a thromboembolic event.
The possible presence of such risk factors should always be considered in patients with congenital and acquired hemophilia.
FEIBA NF should be used with particular caution and only if there are no therapeutic alternatives in patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, DIC, arterial or venous thrombosis, post-operative immobilization, elderly patients and neonates.
If signs or symptoms of thrombotic and thromboembolic events are observed, 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.

Therapy monitoring

Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients receiving more than 100 U/kg body weight must be monitored for the development of DIC and/or acute coronary ischemia.. High doses of FEIBA NF should be administered only as long as strictly necessary – in order to stop a hemorrhage.

If clinically significant changes in blood pressure or pulse rate, respiratory distress, coughing or chest pain occur, the infusion is to be discontinued immediately and appropriate diagnostic and therapeutic measures are to be initiated. Significant laboratory parameters for DIC are a drop in fibrinogen, a drop of the thrombocyte count and/or the presence of fibrin/fibrinogen degradation products (FDP). Other parameters for DIC are a clearly prolonged thrombin time, prothrombin time or aPTT. In patients with inhibitor hemophilia or with acquired inhibitors to factors VIII, IX and/or XI, the aPTT is prolonged by the underlying disease.

Patients with inhibitor hemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA NF, may have increased bleeding tendency as well as increased risk of thrombosis at the same time.

Laboratory tests and clinical efficacy

In vitro tests, such as aPTT, whole blood coagulation time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalize these values by increasing the dose of FEIBA NF cannot be successful, and are even to be strongly rejected because of the possible risk of triggering a DIC through overdosing.

Significance of the thrombocyte count

If the response to treatment with FEIBA NF is inadequate, conducting a thrombocyte count is recommended since a sufficient number of functionally intact thrombocytes is necessary for the efficacy of FEIBA NF.

PRECAUTIONS

Thromboembolic Complications

In the following situations, FEIBA NF is to be applied only if no reaction to treatment with suitable blood coagulation factor concentrates can be expected – e.g. in case of a high inhibitor titer and a life-threatening hemorrhage or risk of bleeding (e.g. post-traumatically or postoperatively):

- Disseminated intravascular coagulation (DIC): laboratory findings and/or clinical symptoms
- Liver damage: Due to the delayed clearance of activated coagulation factors, patients with impaired liver function are at increased risk of developing DIC.
- Coronary heart disease, acute thrombosis and/or embolism.

Patients who receive FEIBA NF should be monitored for the development of DIC, acute coronary ischemia, and signs and symptoms of other thromboembolic events. At the first signs or symptoms of thrombotic and thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

Discordant Response to Bypassing Agents

Due to patient-specific factors the response to a bypassing agent can vary, and in a given bleeding situation patients experiencing insufficient response to one agent may respond to another agent. In case of insufficient response to one bypassing agent, use of another agent should be considered.

Anamnestic Responses

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.

Hepatitis B Surface Antibodies and Test Interpretation

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.

Pediatrics

Case reports and limited clinical trial data suggest that FEIBA NF can be used in children younger than 6 years of age. The same dose regimen as in adults should be adapted to the child's clinical condition.

Prophylactic use in hemophilia B patients with inhibitors

Due to the rarity of the disease, only limited clinical data is available for the prophylaxis of bleeding in hemophilia B patients (literature case reports, n = 4, and clinical data in prophylaxis study 090701, n = 1).

Transmission of infectious agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

It is strongly recommended that every time that FEIBA NF is administered to the 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.
Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/ repeated receipt of human plasma-derived products including FEIBA NF.

Excipient related considerations

FEIBA NF contains approximately 4 mg sodium (calculated) per ml; it is approx. 80 mg sodium for the presentation 500 U and 1000 U FEIBA NF. This is to be taken into consideration in patients on a low sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

No adequate and well-controlled studies of the combined or sequential use of FEIBA NF and recombinant Factor VIIa or antifibrinolytics have been conducted. The possibility of thromboembolic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA NF. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA NF.
In cases of concomitant rFVIIa use a potential drug interaction cannot be excluded according to available in vitro data and clinical observations (potentially resulting in adverse events such as thromboembolic event).

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of FEIBA NF in pregnant or lactating women. Physicians should balance the potential risks and only prescribe FEIBA NF 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.
No animal reproduction studies have been conducted with FEIBA NF, and the effects of FEIBA NF on fertility have not been established in controlled clinical trials.

4.7 Effects on the ability to drive and use machines

FEIBA NF has no, or negligible, influence on the ability to drive or to use machines.

4.8 Undesirable effects

The adverse reactions presented in this section have been reported from post marketing surveillance as well as from 2 studies with FEIBA NF for the treatment of bleeding episodes in pediatric and adult patients with hemophilia A or B and inhibitors to factors VIII or IX. One study also enrolled acquired hemophilia patients with factor VIII inhibitors (2 of 49 patients). The adverse reactions from a third study comparing prophylaxis with on-demand treatment have been added.

Frequency categories are defined according t the following convention:

very common	≥ 1/10
common	≥ 1/100 to <1/10
uncommon	≥ 1/1,000 to <1/100
rare	≥ 1/10,000 to <1/1,000
very rare	< 1/10,000
unknown	cannot be estimated from the available data

Adverse Reactions		
System organ class (SOC)	**Preferred MedDRA (version 15.1) Term**	**Frequency* Category**
Blood and lymphatic system disorders	Disseminated intravascular coagulation (DIC) Increase of inhibitor titer (anamnestic response)[a]	Unknown Unknown
Immune system disorders	Hypersensitivity [c] Urticaria Anaphylactic reaction	Common Unknown Unknown
Nervous system disorders	Paresthesia Hypaesthesia Thrombotic stroke Embolic stroke Headache[c] Somnolence Dizziness[b] Dysgeusia	Unknown Unknown Unknown Unknown Commonn Unknown Common Unknown
Cardiac disorders	Cardiac infarction Tachycardia	Unknown Unknown
Vascular disorders	Thrombosis, Venous thrombosis Arterial thrombosis Embolism (thromboembolic complications) Hypotension[c] Hypertension Flushing	Unknown Unknown Unknown Unknown Common Unknown Unknown
Respiratory, Thoracic, and Mediastinal disorders	Pulmonary embolism Bronchospasm Wheezing Cough Dyspnea	Unknown Unknown Unknown Unknown Unknown
Gastrointestinal disorders	Vomiting Diarrhea Abdominal discomfort Nausea	Unknown Unknown Unknown Unknown
Skin and subcutaneous tissue disorders	Sensation of numbness in the face Angioedema Urticaria Pruritus Rash[c]	Unknown Unknown Unknown Unknown Common
General disorders and administration site conditions	Pain at the injection site Malaise Feeling hot Chills Pyrexia Chest pain Chest discomfort	Unknown Unknown Unknown Unknown Unknown Unknown Unknown
Investigations	Drop in blood pressure Hepatitis B surface antibody positive[c]	Unknown Common

[*] A precise estimate of the rate of these adverse reactions is not possible from the available data.
[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 NF. See Section 4.4.
[b] ADR reported in the original and prophylaxis studies. Frequency shown is from the prophylaxis study only.
[c] ADR reported in the prophylaxis study. Frequency shown is from the prophylaxis study

Class Reactions

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of FEIBA NF is important. It allows continued monitoring of the benefit/risk balance of FEIBA NF. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 OVERDOSAGE

Some of the reported thromboembolic events occurred with doses above 200 U/kg. If signs or symptoms of thromboembolic events are observed, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated. See Section 4.4

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: blood coagulation factors, **ATC code:** B02BD03.

Although FEIBA NF was developed in the early seventies and its factor VIII inhibitor bypassing activity has been proven in vitro as well as in vivo, its mode of action is still the subject of scientific discussion. FEIBA NF, as found with activity assays, is composed of prothrombin complex zymogens which are both procoagulant (prothrombin FVII, FIX, FX) and anticoagulant (protein C) in relatively equal quantities to the arbitrary FEIBA NF potency unit but its procoagulant enzyme content is relatively low. FEIBA NF, thus, contains the proenzymes of the prothrombin complex factors, but only very small amounts of their activation products, with the contents of FVIIa being the highest. [Turecek PL and Schwarz HP. Chapter 4: Factor Eight Inhibitor Bypassing Activity, in Production of Plasma Proteins for Therapeutic Use, eds. Joseph Bertolini, Neil Goss, John Curling, Wiley 2013, ISBN: 978-0-470-92431-0].

Current scientific works point to the role of specific components of the activated prothrombin complex, prothrombin (F II) and activated factor X (FXa) in the mode of action of FEIBA NF. [Turecek PL, Varadi K, Gritsch H, et al. Factor Xa and Prothrombin: Mechanism of Action of FEIBA NF. Vox Sang. 77: 72-79, 1999]
FEIBA NF controls bleeding by induction and facilitation of thrombin generation, a process for which the formation of the prothrombinase-complex is crucial. A number of biochemical in vitro and in vivo studies have shown that FXa and prothrombin play a critical role in the activity of FEIBA NF. The prothrombinase complex has been found to be a major target site for FEIBA NF. Apart from prothrombin and FXa, FEIBA NF contains other proteins of the prothrombin complex, which could also facilitate haemostasis in haemophilia patients with inhibitors.

Treatment of hemophilia B patients with inhibitors
The experience in hemophilia B patients with factor IX inhibitors is limited due to the rarity of the disease. Five hemophilia B patients with inhibitors were treated with FEIBA NF during clinical trials either on-demand, prophylactically or for surgical interventions:

In a prospective open-label, randomized, parallel clinical study in hemophilia A or B patients with persistent high-titer inhibitors (090701, PROOF), 36 patients were randomized to either 12 months ± 14 days of prophylactic or on-demand therapy. The 17 patients in the prophylaxis arm received 85 ± 15 U/kg FEIBA NF administered every other day and the 19 patients in the on-demand arm were treated individually determined by the physician. Two hemophilia B patients with inhibitors were treated in the on-demand arm and one hemophilia B patient was treated in the prophylactic arm.
The median ABR (annualized bleeding rate) for all types of bleeding episodes in patients in the prophylaxis arm (median ABR = 7.9) was less than that of patients in the on-demand arm (median ABR = 28.7), which amounts to a 72.5% reduction in median ABRs between treatment arms.

In another completed prospective non-interventional surveillance study of the perioperative use of FEIBA NF (PASS-INT-003, SURF) a total of 34 surgical procedures were performed in 23 patients. The majority of patients (18) were congenital hemophilia A patients with inhibitors, two were hemophilia B patients with inhibitors and three were patients with acquired hemophilia A with inhibitors. The duration of FEIBA NF exposure ranged from 1 to 28 days, with a mean of 9 days and a median of 8 days. The mean cumulative dose was 88,347 U and the median dose was 59,000 U. For hemophilia B patients with inhibitors, the longest exposure to FEIBA NF was 21 days and the maximum dose applied was 7324 U.

In addition 36 case reports are available when FEIBA NF was used for treatment and prevention of bleeding episodes in hemophilia B patients with factor IX inhibitor (24 hemophilia B patients with inhibitors were treated on-demand, four hemophilia B patients with inhibitors were treated prophylactically and eight hemophilia B patients with inhibitors were treated for surgical procedures).

There are also isolated reports on the use of FEIBA NF in the treatment of patients with acquired inhibitors to factors X, XI and XIII.

5.2 Pharmacokinetic properties

As the mode of action of FEIBA NF is still being discussed, it is not possible to make a conclusive statement about the pharmacokinetic properties.

5.3 Preclinical Safety data

Based on acute toxicity studies with factor VIII knockout mice and normal mice and rats with higher doses than the maximum daily dose for humans (> 200 U/kg of body weight), it can be concluded that the side effects in connection with FEIBA NF mainly result from hypercoagulation due to the pharmacological properties.

Toxicity studies with repeated administration in animal experiments are practically unfeasible as interference occurs through the development of antibodies to heterologous proteins.

Since human blood coagulation factors are not seen as carcinogenic or mutagenic, experimental animal studies, especially in heterologous species, were not considered necessary.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Powder: Sodium chloride
Sodium citrate

Solvent: Sterilized Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except the solvent mentioned in Section 6.6.
As in all blood coagulation preparations, the efficacy and tolerance of the medicinal product may be impaired by being mixed with other medicinal products. It is advisable to rinse a common venous access with a suitable solution, e.g. with isotonic saline solution, before and after the administration of FEIBA NF.
Coagulation factors derived from human plasma may be adsorbed by the inner surfaces of certain types of injection/infusion devices. If this were to occur, it could result in failure of therapy. Therefore, only approved plastic infusion devices may be used with FEIBA NF.

6.3 Shelf life of the reconstituted product

Chemical and physical stability of the reconstituted product has been demonstrated for 3 hours at a temperature of 20°C –25°C.
From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination (controlled and validated aseptic conditions), the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Reconstituted product must not be refrigerated.

6.4 Special Precautions for Storage

Do not store above 25° C. Do not freeze

Store in the original package to protect contents from light.

For storage conditions of the reconstituted medicinal product – see Section 6.3.

Store out of the reach of children.

6.5 Nature and contents of the container

Powder and solvent come in glass vials made of surface-treated, colourless glass (hydrolytic class II). The product vial is closed with a chlorobutyl rubber stopper, while the solvent vial is closed with a bromobutyl rubber stopper.

Each package contains either:

- 1 rubber-capped vial of FEIBA NF 500 or 1000 U (powder for reconstituting solution for intravenous administration).
- 1 rubber-capped vial containing 20 ml sterile water for injections.
- 1 disposable syringe (20 ml capacity).
- 1 disposable needle.
- 1 butterfly needle with clamp (winged set for injection).
- 1 filter needle.
- 1 transfer needle.
- 1 aeration needle.

or

1 rubber-capped vial with FEIBA NF – powder for solution for intravenous administration
1 rubber-capped vial with 20 ml sterilised Water for Injections
1 Baxject II Hi-Flow – Needleless transfer device intended for transferring and mixing drugs contained in two vials into a syringe
1 disposable syringe
1 disposable needle
1 butterfly needle with clamp (winged set for injection)

6.6. Special precautions for disposal and other handling advice

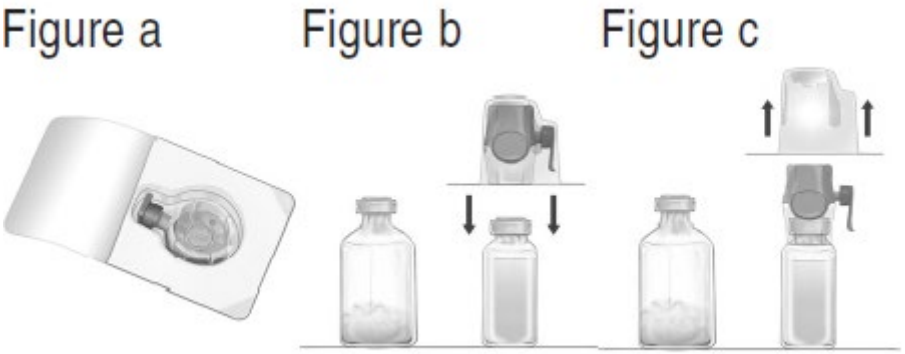
To prepare the FEIBA NF solution, use only the sterilised water for injections and the reconstitution device provided in the pack. Use aseptic technique throughout entire procedure. FEIBA NF is to be reconstituted only immediately before administration. The solution should then be used straight away (the solution does not contain preservatives). Swirl gently until all material is dissolved. Ensure that FEIBA NF is completely dissolved; otherwise, less FEIBA NF Units will pass through the device filter. After reconstitution, the solution should be inspected for particulate matter and discoloration prior to administration.

Do not use solutions which are cloudy or have deposits. Open containers must not be re-used. Do not use if the needleless transfer device or the transfer needle, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.
Use only the included sterilized Water for Injections and the included device set for reconstitution. If devices other than those enclosed are used, ensure the use of an adequate filter with a pore size of at least 149 µm.

Any unused medicinal product or waste material is to be disposed of in accordance with national requirements.

RECONSTITUTION OF THE POWDER FOR SOLUTION FOR INJECTION WITH THE BAXJECT II HI-FLOW:

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 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.



Instructions for 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)

Figure d

Figure e

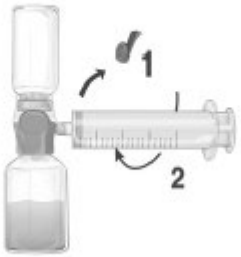


Figure f

Do not exceed an injection speed of 2 U FEIBA NF/kg body weight per minute.

RECONSTITUTION OF THE POWDER TO PREPARE A SOLUTION FOR INJECTION WITH TRANSFER NEEDLE:

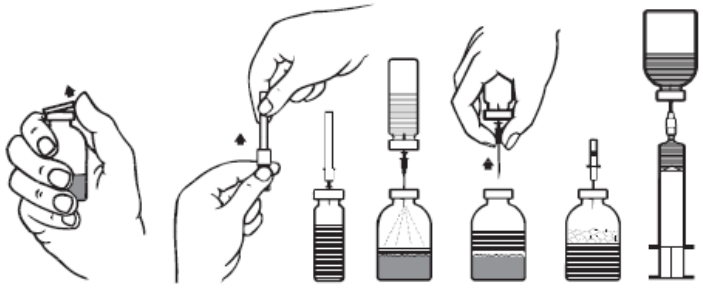
1. Warm the unopened vial containing the solvent (sterile water for injections) to room temperature, e.g. using a sterile water bath for warming within several minutes (max. +37°C).
2. Remove protective caps from the concentrate vial and solvent vial (fig. 1) and disinfect the rubber stoppers of both 2 vials.
3. Remove protective covering from one end of the supplied "transfer needle" by twisting and pulling (fig. 2). Insert the exposed needle through the rubber stopper of the solvent vial (fig. 3).
4. Remove protective covering from the other end of the transfer needle taking care not to touch the exposed end.
5. Invert the solvent vial over the concentrate vial, and insert the free end of the transfer needle through the rubber stopper of the concentrate vial (fig. 4). The solvent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing the needle from the concentrate vial (fig. 5). Gently agitate or rotate the concentrate vial to accelerate dissolution.
7. Upon complete reconstitution of the concentrate, insert the enclosed "aeration needle" provided (fig. 6) and any foam will collapse. Remove aeration needle.

INJECTION/INFUSION:

1. Remove protective covering from the supplied "filter needle" by twisting and pulling and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. 7).
2. Disconnect the filter needle from the syringe and slowly inject the solution intravenously by means of the enclosed infusion set (and disposable needle, respectively).

Do not exceed an injection/infusion rate of 2 units FEIBA NF per kg of body weight per minute.
After injection/infusion: put all needles together with the syringe and/or the venepuncture instruments into the product box without closing them to avoid endangering other persons.

The administration of the preparation must be documented by means of the attached adhesive labels in the anamnesis.



7. REGISTRATION NUMBERS:
FEIBA NF 500 Units: 026 14 25389 00
FEIBA NF 1000 Units: 026 15 25390 00

8. MANUFACTURER
Baxter AG
Industriestrasse 67
A-1220 Vienna, Austria.

9. LICENCE HOLDER
Takeda Israel Ltd.,
25 Efal st., Petach Tikva 4951125.