Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

FEIBA 1000 U

Powder and solvent for solution for injection or infusion

Active ingredient
Each vial of FEIBA 1000U contains 1000 units of Factor VIII inhibitor bypassing fraction

Inactive ingredients and allergens: See 'Important information about some of this medicine's ingredients' in section 2, and section 6 'Additional information'.
Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. What is this medicine intended for?

- Controlling bleeding in hemophilia A patients with Factor VIII Inhibitors (antibodies) and also in patients with acquired Factor VIII Inhibitors.
- Controlling bleeding in hemophilia B patients with inhibitors, if no other specific treatment is available.

Therapeutic group: blood clotting agents.
FEIBA is a preparation made from human plasma which allows stopping and preventing bleeding (hemostasis), even when individual coagulation factors are reduced or absent.

2. Before using this medicine

Do not use this medicine

In the following conditions, if there are alternative therapeutic options:

- if you are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine (listed in section 6)
- if a disseminated intravascular coagulation (DIC) exists. (DIC is a consumption coagulopathy, a life-threatening condition in which excessive blood coagulation with pronounced blood clot formation in the blood vessels occurs. This then leads to a consumption of the coagulation factors in the entire body).
- in case of acute thrombosis and/or embolism (including myocardial infarction)

Special warnings about using this medicine

Talk to your doctor before using FEIBA, because hypersensitivity reactions may occur, as is the case with all intravenously administered plasma products. To be able to recognize an allergic reaction as soon as possible, you should be aware of potential early symptoms of a hypersensitivity reaction such as:
– erythema (reddening of the skin)
– skin rash
– occurrence of hives on the skin (nettle rash/urticaria)
– itching over the entire body
– swelling of lips and tongue
– breathing difficulties/breathlessness
– tightness of the chest
– general indisposition
– dizziness
– drop of blood pressure

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

If you notice one or more of these symptoms, stop the injection/infusion immediately and contact your doctor straight away. The above mentioned symptoms may be early indications of anaphylactic shock. Severe symptoms require prompt emergency treatment.

Your doctor will only re-use FEIBA in patients with suspected hypersensitivity to the product or any of its components after carefully weighing the expected benefit and the risk of re-exposure and/or no reaction with another preventative therapy or alternative therapeutic agents is expected.

- If you notice major changes in blood pressure or pulse rate, breathing difficulties, coughing or chest pain, stop the infusion immediately and contact your doctor. Your doctor will initiate the appropriate diagnostic and therapeutic measures.
- Patients with inhibitor hemophilia or acquired inhibitors to coagulation factors: Under treatment with FEIBA, these patients may have an increased bleeding tendency and an increased risk of thrombosis at the same time.

Thrombotic and thromboembolic events, including disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA. Concomitant use of recombinant Factor VIIa likely increases the risk of developing a thromboembolic event. Some of the thromboembolic events occurred in cases of treatment with high doses of FEIBA.

In a study performed by another company to evaluate emicizumab (a medicine to prevent bleeding in patients with hemophilia A), some patients who suffered from breakthrough bleeds were treated with FEIBA to control the bleeds, and a few of these patients developed thrombotic microangiopathy (TMA). TMA is a serious and potentially life-threatening side effect. When people have this side effect, the lining of the blood vessels can be damaged and blood clots may develop in small blood vessels. In some cases, this can cause damage to the kidneys and other organs. In case of breakthrough bleeds while on emicizumab prophylaxis, contact your hemophilia doctor or Hemophilia Treatment Center immediately.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/ infections. The manufacturing process of these products also includes steps in the processing of the blood and plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to unknown or emerging viruses and other types of infections.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. 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 whose immune system is depressed or who have some types of anemia (such as sickle cell disease or hemolytic anemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly or repeatedly receive human plasma-derived Factor VIII inhibitor products.

Tests and follow-up
After administration of high doses of FEIBA, the transitory rise of passively transferred Hepatitis B surface antibodies may result in misleading interpretation of positive results in serological testing.
FEIBA is a plasma derived product and could contain substances that react when injected/infused in patients, causing the presence of isohemagglutinins (antibodies that cause the adhesion of red blood cells from another person). This process can lead to misleading results in blood tests.
It is strongly recommended that every time you receive a dose of FEIBA the name and batch number of the product are recorded in order to maintain a record of the batches you used.

Other medicines and FEIBA

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

No adequate and well-controlled studies of the combined or sequential use of FEIBA and recombinant Factor VIIa, antifibrinolytics or emicizumab have been conducted. The possibility of thrombotic events should be considered when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. Therefore, antifibrinolytics should not be used for approximately 6 to 12 hours after the administration of FEIBA.

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 a thromboembolic event. Tell your doctor if you are about to be treated with FEIBA after receiving emicizumab (a medicine to prevent bleeding in patients with hemophilia A) as there are specific warnings and precautions to be considered. Your doctor will need to monitor your condition closely.

As in all blood coagulation preparations, FEIBA should not be mixed with other medicines before administration, as the efficacy and tolerance of the preparation may be impaired.
It is advisable to rinse a common venous access with a physiological saline solution before and after the administration of FEIBA.

Pregnancy, breastfeeding, and fertility
Your doctor will decide if FEIBA may be used during pregnancy and breastfeeding. Due to the increased risk of thrombosis during pregnancy, FEIBA should be administered only under careful medical monitoring and only if absolutely necessary. Information about parvovirus B19 infection is given in section 2, ‘Special warnings about using this medicine’.

Driving and using machines
There are no signs that FEIBA may affect the ability to drive or to use machines.

Important information about some of this medicine’s ingredients
FEIBA contains 80 mg sodium (the main component of table/cooking salt) in each vial. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions.
Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Reconstitute (dissolve) the freeze-dried FEIBA powder with the enclosed solvent and administer the solution intravenously. **See detailed instructions for use at the end of this leaflet.**

Your doctor determines the dose and dosage intervals that you personally require by taking into consideration the severity of your blood coagulation disorder, the location and extent of the hemorrhage, and your general condition and response to the preparation. Do not change the dosage established by your doctor, and do not discontinue using the preparation independently.

Talk to your doctor or pharmacist if you think that the effect of FEIBA is too strong or too weak.

Do not exceed the recommended dose.

Warm the product to room or body temperature prior to administration if necessary.

Prepare the FEIBA solution immediately prior to administration. The solution should be used immediately (as the preparation does not contain preservatives).

Swirl gently (by rotating the vial) until all material is dissolved. Ensure that FEIBA is completely dissolved; otherwise, less FEIBA units will pass through the device filter.

Solutions that are cloudy or contain deposits should to be disposed of appropriately.

Do not reuse opened containers.

Use only the enclosed water for injections and the enclosed accessory set for reconstitution (dissolving).

If accessories other than those enclosed are used, ensure use of a suitable filter with at least 149 µm pore size.

Do not use the product if its sterile barrier has been breached, its package is damaged or if it shows signs of wear.

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

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

If you use more FEIBA than you should:

inform your doctor immediately. Overdosage of FEIBA may increase the risk of undesired events, such as thromboembolism (formation of a blood clot that washes into the blood vessels), consumption coagulopathy (DIC) or myocardial infarction. Some of the reported thromboembolic events occurred with doses above 200 U/kg or in patients with other risk factors for thromboembolic events. If signs or symptoms of thrombotic and thromboembolic events are observed, **the infusion should be stopped immediately** and appropriate diagnostic and therapeutic measures initiated.
Adhere to the treatment as recommended by the doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

Like with all medicines, using FEIBA may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

- **Common side effects** (may affect up to 1 in 10 people):
  hypersensitivity, headache, dizziness, low blood pressure, rash, hepatitis B surface antibody positive.

- **Side effects of unknown frequency** (the frequency of these effects has not been established yet):

- **Blood and lymphatic system disorders:** consumption coagulopathy (DIC), increase of inhibitor titer (level).
- **Immune system disorders:** anaphylactic reactions, nettle-rash over the entire body (urticaria).
- **Nervous system disorders:** feeling of numbness in the limbs (hypoesthesia), abnormal or reduced sensation (paresthesia), stroke (thrombotic stroke, embolic stroke), sleepiness (somnolence), altered sense of taste (dysgeusia).
- **Cardiac disorders:** heart attack (myocardial infarction), palpitations (tachycardia).
- **Vascular disorders:** blood clot formation with flushing into the vessels (thromboembolic events, venous and arterial thrombosis), increased blood pressure (hypertension), flushing.
- **Respiratory, thoracic, and mediastinal disorders:** obstruction of the pulmonary artery (pulmonary embolism), constriction of the air passages (bronchospasm), wheezing, cough, breathlessness (dyspnea).

- **Gastrointestinal disorders:** vomiting, diarrhea, abdominal discomfort, nausea.
- **Skin and subcutaneous tissue disorders:** feeling of numbness in the face, swelling of face, tongue and lips (angioedema), nettle-rash over the entire body (urticaria), itching (pruritus).
- **General disorders and complaints at the injection site:** pain at injection site, general feeling of being unwell, feeling hot, chills, fever, chest pain, chest discomfort.

Other side effects: Rapid injection or intravenous infusion can cause stabbing pain and a sensation of numbness in face and limbs, as well as a decrease in blood pressure.

Myocardial infarctions were observed after the administration of doses above the maximum daily dose and/or prolonged use and/or the presence of risk factors for thromboembolism.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your doctor.
Do not use the medicine after the expiry date (exp. date) which is stated on the FEIBA package/vial. The expiry date refers to the last day of that month.

The preparation's chemical and physical stability has been demonstrated for 3 hours at room temperature (up to 25°C). From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination (reconstitution under controlled and validated aseptic conditions), the product should be used immediately after reconstitution. If not used immediately, storage conditions and duration are the responsibility of the user.

Reconstituted (dissolved) product must not be placed in the refrigerator.

Storage conditions before reconstitution:
Do not store above 25°C. Do not freeze. Store in the original package to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
sodium chloride, sodium citrate dihydrate.

What the medicine looks like and contents of the pack:
The product is presented as white to off-white or pale green freeze-dried powder or friable solid. The pH-value (acidity) of the ready to use solution is between 6.8 and 7.6. Powder and solvent are supplied in vials made of glass and closed with rubber stoppers.

Each pack contains:
- 1 vial with 1000 units FEIBA powder for solution for injection or infusion
- 1 vial with 20 ml water for injections (solvent)
- 1 BAXJECT II Hi-Flow device
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle with clamp

or

- 1 vial with 1000 units FEIBA powder for solution for injection or infusion
- 1 vial with 20 ml water for injections (solvent)
- 1 disposable syringe
- 1 disposable needle
- 1 butterfly needle with clamp
- 1 filter needle
- 1 transfer needle
- 1 injection needle

Registration holder's name and address: Takeda Israel Ltd., 25 Efal St., Petah Tikva 4951125.

Manufacturer's name and address:

Takeda Manufacturing Austria AG, Industriestrasse 67, A-1221 Vienna, Austria.

This leaflet was revised in October 2021 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health National Drug Registry:

FEIBA 1000 U: 026-15-25390-00

Directions for reconstitution and use

Reconstitution of the powder for preparing a solution for injection or infusion with BAXJECT II Hi-Flow:

Use aseptic techniques throughout the entire procedure!

1. Warm the unopened solvent vial (containing water for injections) to room temperature or up to 37°C, for example by using a water bath for several minutes.
2. Remove the protective caps from the powder vial and solvent vial and disinfect the rubber stoppers of both vials. Place the vials on an even surface.
3. Open the packaging of the BAXJECT II Hi-Flow by pulling off the protective foil without touching the contents of the package (Fig. A). Do not remove the transfer system from the package at this point.
4. Turn the package over and press the transparent plastic pin through the rubber stopper of the solvent vial (Fig. B). Now remove the packaging from the BAXJECT II Hi-Flow (Fig. C). **Do not remove** the blue protective cap from the BAXJECT II Hi-Flow at this point.
5. Now turn the system, consisting of the BAXJECT II Hi-Flow and the solvent vial, in such a way that the solvent vial is on top. Press the purple pin of the BAXJECT II Hi-Flow through the FEIBA vial. The solvent is drawn into the FEIBA vial by vacuum (Fig. D).
6. Swirl gently, but do not shake the entire system until the powder is dissolved. Make sure that FEIBA has been dissolved completely, as active substance may otherwise be retained by the filter in the system.

Fig. A

FIG. B

Fig. C

Injection or infusion
Use aseptic techniques throughout the entire procedure!

1) Remove the blue protective cap from the BAXJECT II Hi-Flow. Tightly connect the syringe to the BAXJECT II Hi-Flow. **DO NOT DRAW AIR INTO THE SYRINGE.** (Fig. E). In order to ensure tight connection between the syringe and BAXJECT II Hi-Flow, the use of a luer lock syringe is highly recommended (turn syringe in clockwise direction until stop position when mounting).
2) Invert the system so that the dissolved product is on top. Draw the dissolved product into the syringe by pulling the plunger back **SLOWLY** and ensure that the tight connection between BAXJECT II Hi-Flow and the syringe is maintained throughout the whole pulling process (Fig. F).
3) Disconnect the syringe.
4) If foam is formed in the syringe, wait until the foam collapses. Slowly administer the solution intravenously with the enclosed infusion set (or disposable needle).

Fig. D

Fig. E

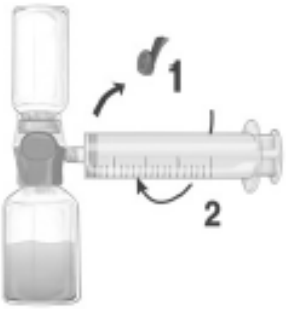

Fig. F

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

Reconstitution of the powder for preparing a solution for infusion with needles:
Use aseptic techniques throughout the entire procedure!

1. Warm the unopened solvent vial (containing water for injections) to room temperature or up to 37°C, for example by using a water bath for several minutes.
2. Remove the protective caps from the powder vial and solvent vial (Fig. A) and disinfect the rubber stoppers of both vials.
3. Twist open the protective cap on one end of the enclosed transfer needle, remove it and insert the needle through the rubber stopper of the solvent vial (Fig. B and Fig. C).
4. Very carefully remove the protective cap from the other end of the transfer needle taking care not to touch the exposed end!
5. Invert the solvent vial and insert the free end of the transfer needle through the rubber stopper of the powder vial (Fig. D). The solvent will be drawn into the powder vial by vacuum.
6. When the solvent has been completely transferred into the powder vial, disconnect the two vials by removing the transfer needle from the powder vial (Fig. E). Gently swirl the powder vial to accelerate dissolution.
7. Upon complete reconstitution (dissolving) of the powder, insert the enclosed aeration needle (Fig. F) to collapse any foam that may have formed. Remove the aeration needle.

Injection or infusion:

Use aseptic techniques throughout the entire procedure!

1. Twist open the protective cap on one end of the enclosed filter needle, remove it and screw the needle on to the sterile disposable syringe. Draw the solution into the syringe (Fig. G).
2. Disconnect the filter needle from the syringe and slowly administer the solution intravenously with the enclosed infusion set (or disposable needle).

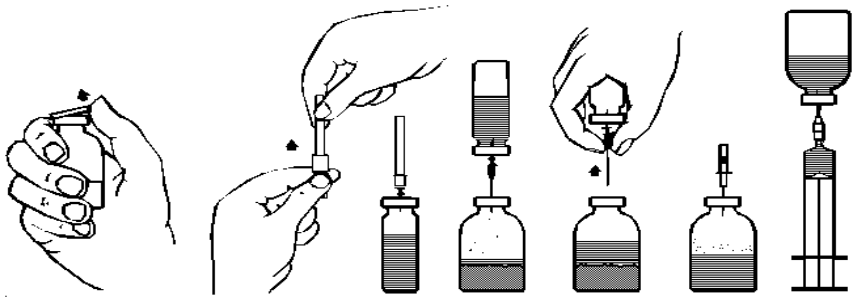

Fig. A Fig. B Fig. C Fig. D Fig. E Fig. F Fig. G

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