PACKAGE LEAFLET: INFORMATION FOR THE USER

FEIBA 100 U/ml powder and solvent for solution for infusion

Factor VIII Inhibitor Bypassing Activity

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHAT FEIBA IS AND WHAT IT IS USED FOR

FEIBA is a preparation made from human plasma which allows hemostasis, even when individual coagulation factors are reduced or absent.

FEIBA is used for the treatment of bleedings in inhibitor haemophilia A patients.

FEIBA is used for the treatment of bleedings in inhibitor haemophilia B patients, if no other specific treatment is available.

FEIBA is also used for prophylaxis of bleeding in inhibitor haemophilia A patients who have experienced a significant bleed or are at high risk of significant bleeding.

Furthermore, FEIBA may be used for the treatment of bleedings in non-hemophilic patients who have acquired inhibitors to factor VIII.

FEIBA can be used for all age groups.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE FEIBA

Please inform your doctor if you have a known allergy.

Please inform your doctor if you are on a low-sodium diet.

Do not use FEIBA

In the following situations FEIBA should only be used if - for example due to a very high inhibitor titre - no response to treatment with the appropriate coagulation factor concentrate can be expected.

- if you are allergic (hypersensitive) to Factor VIII Inhibitor Bypassing Activity or any of the ingredients of this medicine (listed in section 6).

- if a disseminated intravascular coagulation (DIC) exists. (DIC = 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 myocardial infarction, acute thrombosis and/or embolism: FEIBA should only be used in life threatening bleeding episodes.

Warnings and precautions

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/dyspnoea
- 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 infusion immediately and contact your doctor straight away. The above-mentioned symptoms may be early indications of an 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 careful weighing of the expected benefit and the risk of re-exposure and/or no reaction with another preventative therapy or alternative therapeutic agents is to be expected.

– if you experience 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.
– in patients with inhibitor haemophilia 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 have occurred in case 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 haemophilia 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 condition. When people have this condition, 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 haemophilia treater or Haemophilia 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. Manufacturers of these products also include 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 or 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 anaemia (e.g. sickle cell disease or haemolytic anaemia).

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.

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 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 used.

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.

Other medicines and FEIBA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

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 to be treated with FEIBA after you have received emicizumab (a medicine to prevent bleeding in patients with haemophilia A) as there are specific warnings and precautions to be considered. Your doctor will need to monitor you closely.

As in all blood coagulation preparations, FEIBA should not be mixed with other medicinal products 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, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Your doctor will decide if FEIBA may be used during pregnancy and breast-feeding. 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 warnings and precautions.

Driving and using machines

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

FEIBA contains Sodium

500 U
This medicine contains approximately 40 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult.

1 000 U
This medicine contains approximately 80 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult.

2 500 U
This medicine contains approximately 200 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 10% of the recommended maximum daily dietary intake of sodium for an adult.

3. HOW TO USE FEIBA

Reconstitute the freeze-dried FEIBA powder with the enclosed solvent and administer the solution intravenously.

Always use FEIBA exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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, your doctor has determined the dose and dosage intervals required for you personally. Do not change the dosage established by your doctor and do not discontinue the application of the preparation independently.

Please talk to your doctor or pharmacist if you have the impression that the effect of FEIBA is too strong or too weak.

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

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

Swirl gently until all material is dissolved. Ensure that FEIBA is completely dissolved; otherwise, less FEIBA Units will pass through the device filter.

Solutions, which are cloudy or have deposits, are to be disposed of appropriately.

Do not reuse opened containers.

Use only the enclosed Water for Injections and the enclosed device set for reconstitution.

If devices 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 damaged or if it shows signs of deterioration.

Do not refrigerate after reconstitution.

After complete reconstitution of FEIBA, its injection or infusion should be commenced immediately and must be completed within three hours following reconstitution.

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

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

1. Warm the unopened solvent vial (Water for Injections) to room temperature or max + 37 °C if necessary, 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 around 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, but do not shake the entire system gently until the powder is dissolved. Make sure that the FEIBA has been dissolved completely, as active material may otherwise be retained by the filter in the system.

Fig. a

Fig. b

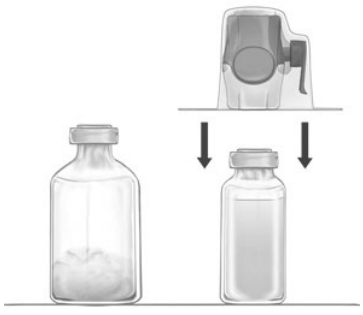
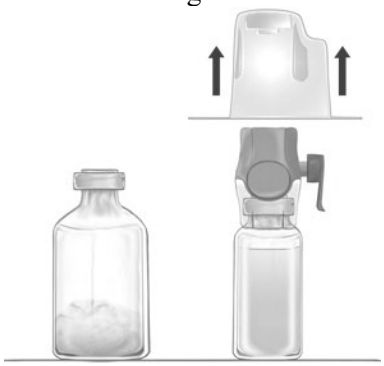


Fig. c



Infusion

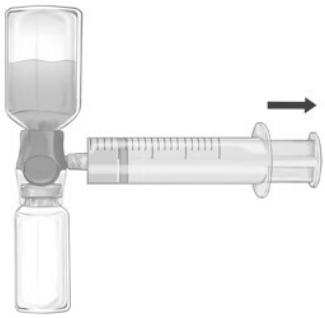
Use aseptic techniques throughout the entire procedure!

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 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 foaming of the product in the syringe occurs, wait until the foam is collapsed. Slowly administer the solution intravenously with the enclosed infusion set.

Fig. d

Fig. e

Fig. f



Do not exceed an infusion rate of 10 U FEIBA/kg body weight per minute.

If you use more FEIBA than you should:

Please inform your doctor immediately. Overdosage of FEIBA may increase the risk of undesired events, such as thromboembolism (formation of a blood clot with flushing into the blood vessels), consumption coagulopathy (DIC) or myocardial infarction. Some of the reported thromboembolic events occurred with doses above 200 U/kg or with 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, FEIBA can cause side effects although not everybody gets them.

Common side effects (may affect up to 1 in 10 people)
Hypersensitivity, Headache, Dizziness, Hypotension, Rash, Hepatitis B surface antibody positive.

Side effects with unknown frequency (the frequency cannot be estimated on the basis of the available data)

Blood and lymphatic system disorders: Consumption coagulopathy (DIC), Increase of inhibitor titer

Immune system disorders: Anaphylactic reactions, Nettle-rash on 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), Palpitation of the heart (Tachycardia)

Vascular disorders: Blood clot formation with flushing into the vessels (thromboembolic events, venous and arterial thrombosis), Increase of 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, Feeling of sickness (Nausea)

Skin and subcutaneous tissue disorders: Feeling of numbness in the face, Swelling of face, tongue and lips (Angioedema), Nettle-rash on 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

Investigations: Drop in blood pressure, increased levels of fibrin D-dimer in blood

Rapid 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 application and/or the presence of risk factors for thromboembolism.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE FEIBA

Keep this medicine out of the sight and reach of children.

Do not store above 25 °C. Do not freeze.
Store in the original package in order to protect from light.

Do not use this medicine after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What FEIBA contains

Powder
- The active substance per vial is factor VIII inhibitor bypassing activity.
- 1 ml contains 100 U factor VIII inhibitor bypassing activity.
- FEIBA 100 U/ml is available in three different presentations:
  - The presentation 500 U FEIBA contains 500 U (Units) factor VIII inhibitor bypassing activity in 200 – 600 mg human plasma protein.
  - The presentation 1 000 U FEIBA contains 1 000 U (Units) factor VIII inhibitor bypassing activity in 400 – 1 200 mg human plasma protein.
  - The presentation 2 500 U FEIBA contains 2 500 U (Units) factor VIII inhibitor bypassing activity in 1 000 – 3 000 mg human plasma protein.

  FEIBA also contains factors II, IX and X, mainly in non-activated form as well as activated factor VII. Factor VIII coagulation antigen (FVIII C:Ag) as well as the factors of the kallikrein-kinin system are present only in trace amounts, if at all.
- The other ingredients are sodium chloride and sodium citrate.

Solvent
- Water for Injections

What FEIBA looks like and contents of the pack

The product is presented as freeze-dried powder or friable solid of white to off-white or pale green color. The pH-value of the ready to use solution is between 6.5 and 7.3.

Powder and solvent are supplied in vials made of glass and are closed with rubber stoppers.

Presentation: 1 x 500 U
1 x 1 000 U
1 x 2 500 U

Not all pack sizes may be marketed.

Content of the pack:

- 1 vial with 500 U / 1 000 U / 2 500 U FEIBA powder for solution for infusion
- 1 vial with 5 ml / 10 ml / 25 ml Water for Injections
- 1 BAXJECT II Hi-Flow for reconstitution
- 1 disposable syringe
- 1 butterfly needle with clamp

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:

Baxalta Innovations GmbH
Industriestrasse 67
1221 Vienna
Austria

Manufacturer:

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

This leaflet was last revised in February 2024.

The following information is intended for medical or healthcare professionals only:

Treatment should be initiated and monitored by a physician experienced in the treatment of coagulation disorders.

Posology

Dosage and duration of treatment depend on the severity of the haemostatic disorder, 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 each individual case.

As a general guideline, a dose of 50 – 100 U FEIBA per kg body weight is recommended; an individual 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.

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.

Paediatric population

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 hemorrhage

A dose of 50 – 75 U/kg body weight at 12-hour intervals is recommended for minor to moderately severe bleeding. The treatment is to be continued until a clear improvement of the clinical symptoms, e.g. reduction 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 hemorrhage

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 hemorrhages

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 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) Prophylaxis in haemophilia A patients with inhibitors

- **Prophylaxis of bleeding in patients with a high inhibitor titer and frequent hemorrhages after failed immune tolerance induction (ITI) or when an ITI is not considered:**
  A dose of 70 – 100 U/kg body weight every other day is recommended. If necessary, the dose may be increased to 100 U/kg body weight per day or it may be decreased gradually.

- **Prophylaxis of bleeding in patients with a high inhibitor titer during an immune tolerance induction (ITI):**
  FEIBA may be administered concomitantly with factor VIII administration, in a dosage range of 50 – 100 U/kg body weight, twice per day, until the factor VIII inhibitor titer has decreased to < 2 B.U. *

  * 1 Bethesda Unit is defined as the amount of antibodies which inhibits 50% factor VIII activity in incubated plasma (2 h at 37 °C).

4) Use of FEIBA in special patient groups

FEIBA was also used in combination with factor VIII concentrate for a long-term therapy to achieve a 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 are 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.

Method of administration

FEIBA is to be administered slowly intravenously. FEIBA should be infused at an infusion rate of 2 U/kg body weight per minute. In patients who have tolerated the infusion rate of 2 U/kg body weight per minute well, in subsequent infusions the rate may be increased up to a maximum of 10 U/kg body weight per minute.
FEIBA is to be reconstituted immediately prior to administration. The solution should be used immediately (as the preparation does not contain preservatives). Do not use solutions which are cloudy or have deposits. Any unused product or waste material should be disposed of in accordance with local requirements.

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 100 U/kg body weight or more must be monitored carefully, particularly for the development of DIC and/or acute coronary ischemia and for symptoms of other thrombotic or thromboembolic events. High doses of FEIBA 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 haemophilia or with acquired inhibitors to factors VIII, IX and/or XI, the aPTT is prolonged by the underlying disease.

Administration of FEIBA to patients with inhibitors may result in an initial anamnestic rise in inhibitor levels. Upon continued administration of FEIBA, inhibitors may decrease over time. Clinical and published data suggest that the efficacy of FEIBA is not reduced.

Patients with inhibitor haemophilia or with acquired inhibitors to coagulation factors, who are treated with FEIBA, 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 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 is inadequate, conducting a thrombocyte count is recommended since a sufficient number of functionally intact thrombocytes is necessary for the efficacy of FEIBA.

Treatment of haemophilia B patients with inhibitors

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

In a prospective open-label, randomized, parallel clinical study in haemophilia 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 administered every other day and the 19 patients in the on-demand arm were treated individually determined by the physician. Two haemophilia B patients with inhibitors were treated in the on-demand arm and one haemophilia 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 (PASS-INT-003, SURF) a total of 34 surgical procedures were performed in 23 patients. The majority of patients (18) were congenital haemophilia A patients with inhibitors, two were haemophilia B patients with inhibitors and three were patients with acquired haemophilia A with inhibitors. The duration of FEIBA 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 haemophilia B patients with inhibitors, the longest exposure to FEIBA was 21 days and the maximum dose applied was 7324 U. In addition, 36 case reports are available when FEIBA was used for treatment and prevention of bleeding episodes in haemophilia B patients with factor IX inhibitor (24 haemophilia B patients with inhibitors were treated on-demand, four haemophilia B patients with inhibitors were treated prophylactically and eight haemophilia B patients with inhibitors were treated for surgical procedures).

The tolerability and safety of FEIBA, reconstituted in regular or 50% reduced volume and of faster infusion rates in haemophilia patients with inhibitors was investigated in a prospective, open-labeled, and randomized crossover study (091501). Thirty-three patients were treated, and twenty-eight patients completed the study. In the study, FEIBA was reconstituted in 50% reduced volume (100 U/ml concentration) and infused IV at infusion rates of 2, 4 and 10 U/kg/min at the labelled dose of 85 U/kg ± 15 U/kg for all patients. The primary endpoints were tolerability and safety with the 50% reduced volume (increased concentration) at standard and increased infusion rates. The study demonstrated that both the higher concentration (100 U/ml) and the higher infusion rates (4 and 10 U/kg/min) were well tolerated and that the safety profile was comparable at the labelled dose of 85 U/kg ± 15 U/kg. The patients who received the 50% reduced volume (increased concentration) at the standard infusion rate of 2 U/kg/min had similar rates of related treatment emergent adverse events (TEAEs) compared to those who received the regular volume (50 U/ml concentration) with the same infusion rate. No related TEAEs were reported at the infusion rate of 4 U/kg/min. Patients who received the 50% reduced volume (100 U/ml) at the infusion rate of 10 U/kg/min experienced 1 related, non-serious TEAE In addition, the patients who received the 50% reduced volume (increased concentration) at the increased infusion rates of 4 and 10 U/kg/min did not experience any serious TEAE, any hypersensitivity reaction, any infusion site reaction, any thrombotic TEAE, or any TEAE leading to drug withdrawal or study discontinuation. Overall, the TEAEs seen in the study were consistent with the known safety profile of FEIBA in patients with haemophilia with inhibitors.

In an open, uncontrolled, non-interventional observational post-authorization safety study of FEIBA (PASS-EU-006), 75 patients (mean age 34.8 years, 70 males and 5 females), of which 73 had haemophilia A with inhibitors and 2 haemophilia B with inhibitors, were treated with FEIBA. Of the 65 patients with congenital haemophilia , 63 had congenital haemophilia A and 2 had congenital haemophilia B. At baseline, 43 patients were prescribed FEIBA for prophylaxis and 32 were prescribed FEIBA for on-demand treatment. Higher infusion rates (> 2 U/kg/min) were used in 6 paediatric patients with age between 11 months and 11 years and in 5 adolescents with age 13 to 16 years.
Out of 320 infusions with an available infusion rate in 7 paediatric and 6 adolescent patients, there were 129 infusions (40.3%) in 2 patients (both paediatric) with infusion rate > 10 U/kg/min, 26 infusions (8.1%) in 7 patients (4 paediatric; 3 adolescents) with infusion rate > 4 and ≤ 10 U/kg/min, 135 infusions (42.2%) in 7 patients (3 paediatric; 4 adolescents) with infusion rate > 2 and ≤ 4 U/kg/min, and 30 infusions (9.4%) in 3 patients (1 paediatric; 2 adolescents) with infusion rate ≤ 2 U/kg/min.

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