PRESCRIBING INFORMATION

This prescribing information is intended for international use only. Please always consult your full country-specific prescribing information as licenses and licensing conditions may vary from country to country.

FEIBA 500 U / 1000 U, powder and solvent for solution for injection
Factor VIII Inhibitor Bypassing Activity

COMPOSITION

Active substance: Factor VIII Inhibitor Bypassing Activity
FEIBA 500 U* [1000 U*] contains 500 U [1000 U] factor VIII bypassing activity in 200 – 600 mg [400 – 1200 mg] human plasma protein.
FEIBA also contains the factors II, IX and X, mainly in non-activated form, as well as activated factor VII. Factor VIII coagulation antigen (F VIII C:Ag) is present at a concentration of up to 0.1 U/1 U FEIBA. The factors of the kallikrein-kinin system are present in trace amounts only, if at all.

Excipients: Powder: sodium chloride, sodium citrate. Solvent: SWFI

* 1 unit of FEIBA shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma by 50% of the buffer value (blank value).

INDICATIONS

- Therapy and prophylaxis of bleeding in haemophilia A patients with inhibitor to factor VIII
- Therapy and prophylaxis of bleeding in haemophilia B patients with inhibitor to factor IX
- Therapy and prophylaxis of bleeding in non-haemophiliacs with acquired inhibitors to factors VIII, IX and XI.

In combination with factor VIII concentrate, FEIBA was also used for long term therapy to achieve complete and permanent elimination of the factor VIII inhibitor.
In three cases FEIBA was also used in patients with an inhibitor to von-Willebrand Factor.

POSOLOGY

Dosage and duration of treatment depend of the severity of the haemostatic disorder, the localisation and the extent of the bleeding and 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. However a single dose of 100 U/kg body weight and a maximum daily dose of 200 U/kg body weight must not be exceeded.

1) Spontaneous Haemorrhage

<u>Joint, muscle and soft tissue haemorrhage</u>
A dose of 50 – 75 U/kg body weight at 12-hour intervals is recommended for minor to moderate bleeds. The treatment is to be continued until clear signs of clinical improvement such as reduction of pain, decrease of swelling or increase of joint mobility, occur.

For major muscle and soft tissue haemorrhage, such as retroperitoneal haemorrhages, 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 haematocrit) is recommended. If bleeding does not stop, the dose may be increased to 100 U/kg body weight, however not exceeding a daily dose of 200 U/kg body weight.

Other severe haemorrhages
In severe haemorrhage, 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
Taking into consideration the maximum daily dose, 50 – 100 U/kg body weight at 6-hour intervals should be administered.

3) Prophylaxis
- Prophylaxis of bleeding in patients with high inhibitor titre and with frequent bleedings in whom ITI (immune tolerance induction) has failed or is not considered:
  A dose of 70 – 100 U/kg body weight every other day is recommended. This dose may be increased up to 100 U/kg body weight every day if the patient continues to bleed or may gradually be decreased.
- Prophylaxis of bleeding in patients with high inhibitor titre undergoing ITI (immune tolerance induction):
  FEIBA may be administered concomitantly with factor VIII concentrates, in a dosage range of 50 – 100 U/kg body weight, twice per day until the factor VIII inhibitor has been reduced to < 2 B.U..*

* 1 Bethesda Unit is defined as that amount of antibody that will inhibit 50% of the FVIII activity of fresh average human plasma after incubation for 2 hours at 37°C.

METHOD OF ADMINISTRATION
Reconstitute the product and slowly inject or infuse it via the intravenous route. An injection speed of 2 U/kg body weight per minute must not be exceeded.

CONTRAINDICATIONS
Depending on therapeutic alternatives, the contraindications below are to be considered relative or absolute.

- Hypersensitivity to the active substance or to any of the excipients.

In the following situations, FEIBA 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 titre and a life-threatening haemorrhage or risk of bleeding (e.g. posttraumatic or postoperative)

- Disseminated intravascular coagulation (DIC):
  when results of laboratory tests and/or clinical symptoms clearly indicates a liver damage, there is an increased risk of developing DIC due to delayed degradation of activated coagulation factors

- Coronary heart disease, acute thrombosis and/or embolism:
  in patients with a tentative or definite diagnosis of coronary heart disease as well as in patients with acute thrombosis and/or embolism, the use of FEIBA should only be used in life-threatening bleeding episodes.

WARNINGS AND PRECAUTIONS
As with any intravenously administered plasma products, allergic type hypersensitivity reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, drop in blood pressure and anaphylactic shock. If these symptoms occur, patients should be advised to discontinue the treatment and to contact their physician immediately. Shock is treated according to the rules of modern shock therapy.

Individual doses of 100 U/kg body weight and daily doses of 200 U/kg body weight must not be exceeded. Patients who receive an individual dose of 100 U/kg body weight are to be monitored carefully, particularly with regard to the development of a DIC or the occurrence of symptoms of acute coronary ischaemia. High doses of FEIBA should be administered only as long as strictly necessary to stop a haemorrhage.

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. Laboratory parameters indicative at DIC are decreased fibrinogen values, decreased platelet count and/or the presence of fibrin/fibrinogen degradation products (FDP).

There is insufficient data in children under 6 years of age to recommend the use of FEIBA. However, inhibitor formation is a common occurrence in haemophilic children undergoing factor VIII replacement therapy. Case studies have shown the successful use of FEIBA in the young age group.

FEIBA contains approx. 80 mg sodium (calculated) per vial. This has to be attended for patients on low sodium diet.

Acquired haemophilia
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 clotting time (WBCT) and thromboelastograms (TEG) as proof of efficacy do not have to correlate with the clinical picture. Therefore, attempts to normalise 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.

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 or 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 any unknown or emerging viruses or other types of infections.
These measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped virus hepatitis A virus (HAV) and Parvovirus B19.
When a pharmaceutical prepared from human plasma is administered regularly / repeatedly, appropriate vaccination (hepatitis A and B) is recommended.

INTERACTIONS
It is not recommended to administer antifibrinolytics, such as epsilon aminocaproic acid, together with FEIBA.
If application of both antifibrinolytics such as epsilon aminocaproic acid and FEIBA is indicated, the interval between the administration of these two products must be at least 6 hours.

PREGNANCY AND LACTATION
Experience regarding the use of FEIBA during pregnancy and breast feeding is not available. Therefore, due to the increased risk of thrombosis during pregnancy, FEIBA should only be used under careful medical monitoring and if no alternative therapy is available.

UNDESIRABLE EFFECTS
Following adverse reactions have been reported during post marketing. The frequency cannot be estimated due to the nature of the data and therefore is categorized as unknown: disseminated intravascular coagulation (DIC), myocardial infarction, injection site pain, hypersensitivity, urticaria, anaphylactic reaction, blood pressure decreased, hypoaesthesia, facial hypoaesthesia, embolism.

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

Rapid intravenous injection or infusion may cause a stabbing pain and numbness in the face and extremities as well as a drop in blood pressure.

OVERDOSE
Overdosage of FEIBA may increase the risk of undesired events such as thromboembolism, DIC or myocardial infarction.

INCOMPATIBILITIES
FEIBA must not be mixed with other medicinal products prior to administration. 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.

Medicinal product subject to medical prescription.

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