PRESCRIBING INFORMATION

This prescribing information is intended for international use only - please always refer to the locally approved Prescribing Information before using the product.

FEIBA 500 U / 1000 U / 2500 U, powder and solvent for solution for injection

COMPOSITION
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 (empty 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 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 unless the severity of bleeding warrants and justifies the use of higher doses.

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 Haemorrhage

Joint, muscle and soft tissue haemorrhage
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.

**CONTRAINDICATIONS**
FEIBA must not be used in the following situations if therapeutic alternatives to FEIBA are available:
- Hypersensitivity to the product or any of the components.
- Disseminated Intravascular Coagulation (DIC).
- Acute thrombosis or embolism (including myocardial infarction).

**WARNINGS AND PRECAUTIONS**
Thromboembolic events, including DIC, venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, have occurred in the course of treatment with FEIBA. 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.
At the first signs or symptoms of thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

FEIBA 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.

At the first sign or symptom of an infusion/hypersensitivity reaction, FEIBA administration should be stopped and medical care initiated as appropriate.

When considering re-exposure to FEIBA 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.

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.

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.

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 prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to any unknown or emerging viruses or other pathogens.

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. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived products including FEIBA.

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)
- Liver damage: patients with impaired liver function are at increased risk of developing DIC.
- Coronary heart disease, acute thrombosis and/or embolism

Patients who receive FEIBA 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 thromboembolic events, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated.

Case reports and limited clinical trial data suggest that FEIBA can be used in children younger than 6 years of age.

Only limited clinical data is available on the application of FEIBA for the prophylaxis of bleeding in hemophilia patients.
INTERACTIONS
The possibility of thromboembolic 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 adverse events such as a thrombotic event.)

PREGNANCY AND LACTATION
There are no adequate data from the use of FEIBA in pregnant or lactating women. Physicians should balance the potential risks and only prescribe FEIBA 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.

UNDESIRABLE EFFECTS
The following adverse reactions have been reported from post marketing surveillance as well as from 2 studies with FEIBA 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.

- common (≥1/100 to <1/10): hypersensitivity, headache, dizziness, hypotension, rash, hepatitis B surface antibody positive
- unknown (cannot be estimated from the available data): DIC, increase of inhibitor titer (anamnestic response), urticaria, anaphylactic reaction, paresthesia, hypoesthesia, thrombotic stroke, embolic stroke, somnolence, dysgeusia, cardiac infarction, tachycardia, thrombosis, venous thrombosis, arterial thrombosis, embolism, hypertension, flushing, pulmonary embolism, bronchospasm, wheezing, cough, dyspnea, vomiting, diarrhea, abdominal discomfort, nausea, sensation of numbness in the face, angioedema, urticaria, pruritus, pain at the injection site, malaise, feeling hot, chills, pyrexia, chest pain, chest discomfort, decreased blood pressure.

INCOMPATIBILITIES
FEIBA must not be mixed with other medicinal products or solvents. 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.

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.

Medicinal product subject to medical prescription.

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