SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FEIBA 1000 U powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FEIBA is presented as powder and solvent to prepare a solution for infusion containing 400-1200 mg human plasma protein with a Factor Eight Inhibitor Bypassing Activity of 1000 U* per vial.

The final solution has an activity of approximately 50 U/ml when reconstituted with 20 ml of Sterilised Water for Injections.

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

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

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.
The product is presented as freeze-dried powder or friable solid of white to off-white or pale green colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of spontaneous bleeding and cover of surgical interventions in haemophilia A patients with Factor VIII inhibitors
- Treatment of spontaneous bleeding and cover of surgical interventions in non haemophiliacs with acquired inhibitors to Factor VIII
- Prophylaxis in haemophilia A patients with high-responding inhibitors and frequent joint bleeding

4.2 Posology and method of administration

1. **4 .1 Therapeutic indications**

• Treatment of spontaneous bleeding and cover of surgical interventi...
Anchor Name: Indications
[Agency W2O - Claudia Alves]

Treatment should be initiated and supervised by a physician experienced in the management of haemophilia.

Posology

The dosage and duration of the therapy is dependent upon the severity of the disorder, the location and extent of the bleeding and the patient´s clinical condition.

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

As a general guide a dose of 50 to 100 U of FEIBA per kg bodyweight (bw) is recommended. **However, a single dose of 100 U/kg bw and a daily dose of 200 U/kg bw should not be exceeded.**

The following table can be used to guide dosing in bleeding episodes and surgery.

Therapeutic indication	Dose (U/kg/bw)	Frequency of doses (hours)
Spontaneous Bleeding		
Joint muscle and soft tissue haemorrhage Minor to moderate bleeding	50-75 U/kg/bw	Repeat every 12 hours. Treatment should be continued until clear signs of clinical improvement, such as relief of pain, reduction of swelling or mobilisation of the joint.
Joint muscle and soft tissue haemorrhage Major bleeding	100 U/kg/bw	Repeat every 12 hours. Treatment should be continued until clear signs of clinical improvement, such as relief of pain, reduction of swelling or mobilisation of the joint.
Mucous membrane bleeding	50 U/kg/bw if haemorrhage does not stop, the dose may be increased to 100 U/kg/bw	Repeat every 6 hours with careful monitoring of the patient (visible bleeding site, repeated measurements of haematocrit).
Other severe haemorrhage (e.g. CNS)	100 U/kg/bw	Repeat every 12 hours. In individual cases FEIBA may be given at intervals of 6 hours until clear clinical improvement is achieved.
Surgery		
Surgery	50-100 U/kg/bw	Repeat at intervals of up to 6 hours, then every 8-12 hours until wound healing.

Bleeding prophylaxis

1. **Anchor Name: 12 hours**
[Agency W2O - Claudia Alves]

Limited experience has been published on the use of FEIBA in haemophilia A patients with high-responding inhibitors before and during immune tolerance induction (ITI) therapy, or after ITI failure.
The posology should be adapted to the patient's bleeding tendency within the following dose range: 50 to 100 U/kg bw from daily to three times a week. When administered during ITI, a daily dose of 50 U/kg bw may be sufficient.

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.

Monitoring
Coagulation tests such as the whole blood clotting time (WBCT), the thromboelastogram (TEG, r-value), and the aPTT usually show only a minor shortening and may not correlate with clinical improvement. For this reason these tests have only very limited value for monitoring FEIBA therapy (see also 4.4).

Method of Administration

Reconstitute the product for administration as described in section 6.6.

The product should be administered via the intravenous route. Inject the solution slowly. The rate of administration should ensure the comfort of the patient, not exceeding a maximum of 2 U/kg bw per minute.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Disseminated Intravascular Coagulation (DIC)

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.

- Laboratory and/or clinical symptoms that are clearly indicative of liver damage: due to the delayed clearance of activated coagulation factors such patients are at an increased risk of developing DIC.
- Myocardial infarction, acute thrombosis and/or embolism: FEIBA should only be used in life threatening bleeding episodes.

4.4 Special warnings and precautions for use

As with any intravenous protein product, allergic-type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, pruritus, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should be advised to discontinue the use of the product immediately and contact their physician. In case of anaphylactic shock, the current medical standards for shock treatment should be observed.

[no notes on this page]

Single doses of 100 U/kg bw and daily doses of 200 U/kg bw should not be exceeded. Patients given single doses of 100 U/kg bw should be monitored for the development of DIC or symptoms of acute coronary ischaemia. High doses of FEIBA should be given only as long as absolutely necessary to stop bleeding.

Where there are significant clinical changes in blood pressure, pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped immediately and appropriate diagnostic and therapeutic measures initiated. Laboratory results indicative of DIC are decreased fibrinogen value, decreased platelet count, and/or presence of fibrin/fibrinogen degradation products (FDP).

In vitro tests to control efficacy such as aPTT, whole blood clotting time (WBCT) and thromboelastogram (TEG) may not correlate with clinical improvement. For this reason, attempts to normalise these values by increasing the dose of FEIBA may not be successful and are strongly discouraged because of the potential hazard of inducing DIC by overdosage.

In case of inadequate response to FEIBA it is recommended that a platelet count be performed, since a sufficient number of functionally intact platelets is considered to be necessary for the efficacy of FEIBA.

Anamnestic responses with rise in Factor VIII inhibitor titre have been observed in about 20% of patients treated with FEIBA alone; however, these did not appear to interfere with the efficacy of FEIBA.

As FEIBA contains 81.7 mg of sodium per vial, it should be accounted for in patients on a low sodium diet.

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 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 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 red cell turnover (e.g. in haemolytic anaemia).
Appropriate vaccination should be considered for patients in regular/repeated receipt of plasma derived coagulation concentrates. Vaccination against hepatitis A and hepatitis B is recommended.
The recording of the product name and batch number is strongly recommended following each administration of FEIBA in order to maintain a link between the patient and the batch of the product.

4.5 Interactions with other medicinal products and other forms of interaction

It is not recommended to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA treatment.

[no notes on this page]

If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA is indicated, the products should be administered at least 6 hours apart.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with FEIBA. Based on the rare occurrence of haemophilia in women, 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.
FEIBA should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

The undesirable effects reported in the listing hereafter are based on post-marketing experience for FEIBA. In general, their incidence cannot be estimated from the available data.

The most frequent reports were of anaphylactic and hypersensitivity reactions (such as dyspnoea, bronchospasm, angioneurotic oedema, urticaria, rash, flushing) and disseminated intravascular coagulation.

Blood and lymphatic system disorders
- disseminated intravascular coagulation

Cardiac disorders
- myocardial infarction

General disorders and administration site conditions
- injection site pain
- pyrexia

Immune system disorders
- anaphylaxis, hypersensitivity reactions (including allergic reactions), urticaria

Nervous system disorders
- paraesthesia

Vascular disorders
- hypotension
- thromboembolic complications such as thrombosis, ischaemic stroke, vena cava thrombosis, pulmonary embolism, and intracardiac thrombosis

Rapid intravenous injection or infusion may cause injection site pain and paraesthesia as well as a decrease in blood pressure.

[no notes on this page]

Myocardial infarction was found to occur after doses exceeding the recommended maximum daily dose and/or prolonged administration and/or in the presence of risk factors predisposing to thromboembolic disease. The incidence of thrombotic events (including myocardial infarction, DIC, cerebrovascular thrombosis, pulmonary embolism) has been estimated at 8.2 per 100,000 infusions with a 95% confidence interval of [4.7-13.4] per 100,000 infusions.

For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

Biological and/or clinical signs of DIC, myocardial infarction or thromboembolic complications have been observed following the administration of high doses of FEIBA. In such cases administration of the product should be stopped promptly (see also 4.4).

5 PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: activated prothrombin complex against factor VIII antibodies, ATC Code: B02B D03

Although FEIBA was developed in the early 1970s and its factor VIII inhibitor bypassing activity has been demonstrated both in vitro and in vivo, its active principle is still the subject of scientific debate. However, recent scientific work indicates a role of specific components of the activated prothrombin complex, zymogen prothrombin (F II) and activated Factor X (FXa), in the FEIBA mode of action.

5.2 Pharmacokinetic properties

Since FEIBA is composed of different coagulation factors, with varying half-lives for the single components, it is not possible to make any definite statement with regard to the pharmacokinetic properties of FEIBA.

5.3 Preclinical safety data

Based on the acute toxicity studies in factor VIII knockout mice and in normal mice and rats with doses exceeding the maximum daily dose in humans (i.e. >200 U/kg bw), it can be concluded that adverse effects related to FEIBA are primarily the result of hypercoagulation induced by the pharmacological properties of the product.

Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.

Since human plasma proteins are not seen to cause tumorigenic or mutagenic effects, experimental studies particularly in heterologous species are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

[no notes on this page]

6.1 List of excipients

Powder
Sodium Chloride
Sodium Citrate
Protein

Solvent
Sterilised Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or solvents. Only the provided infusion sets should be used.

It is advisable to rinse a common venous access with isotonic saline prior to and after infusion of FEIBA.

6.3 Shelf life

2 years. The reconstituted solution should be used immediately.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze.
Keep container in the outer carton in order to protect from light.

Within the indicated shelf life, FEIBA may be stored at room temperature (+25°C) for a period of 6 months. Record the revised expiry date at the start of the period of storage at room temperature below the expiry date indicated on the product package. At the end of this period the product must be used or discarded. Do not return to the fridge following storage at room temperature.

6.5 Nature and contents of container

FEIBA powder and solvent are supplied in vials (hydrolytic Type II surface treated soda lime glass) closed with halogenobutyl rubber stoppers and protective caps.

Each pack contains 1 vial each of FEIBA powder and solvent, 1 filter needle, 1 transfer needle and an aeration needle.

Not all pack types may be marketed.

6.6 Special precautions for disposal

FEIBA should be reconstituted just prior to administration. The solution should then be used immediately as the preparation contains no preservatives. Do not use solutions that are cloudy or have deposits.

[no notes on this page]

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

Reconstitution of powder: use aseptic technique as described below

1. Warm the unopened vial containing the solvent (sterilised water for injections) to room temperature.
2. Remove the protective caps from the FEIBA and solvent vials (fig. 1) and cleanse the rubber stoppers of both.
3. Remove the 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 the 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 FEIBA vial, and insert the free end of the transfer needle through the rubber stopper of the vial (fig. 4). The solvent will be drawn into the powder vial by vacuum.
6. Disconnect the two vials by removing the needle from the FEIBA vial (fig. 5). Gently swirl the FEIBA vial to dissolve the powder.
7. Upon complete reconstitution insert the enclosed aeration needle provided (fig. 6) and any foam will collapse. Remove aeration needle.

Injection/Infusion:

1. Remove the 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 with a winged set for injection (or a disposable needle).

If devices other than those supplied with FEIBA are used, ensure use of an adequate filter.

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

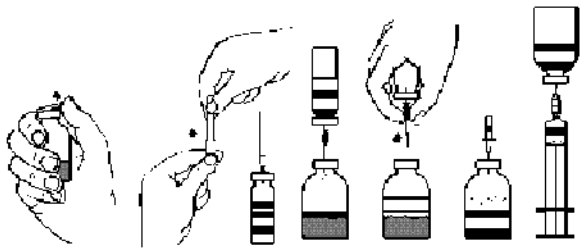

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6 fig. 7

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd
Caxton Way,
Thetford, Norfolk

[no notes on this page]

IP24 3SE
United Kingdom

8 MARKETING AUTHORISATION NUMBERS

PL 00116/0637

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 1985

10 DATE OF REVISION OF THE TEXT

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