FEIBA 500 U & 1000 U POWDER AND SOLVENT FOR SOLUTION FOR INFUSION

(HUMAN PLASMA PROTEINS WITH FACTOR VIII INHIBITOR BYPASSING ACTIVITY)

PL 00215/0021-22

UKPAR

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LAY SUMMARY

The MHRA have granted Immuno Limited authorisation (licence) for a variation to the licence for the medicinal product FEIBA 500 U & 1000 U powder and solvent for solution for infusion, (PL 00215/0021), which is a blood coagulation factor, to update the datasheet to an SPC to comply with current guidelines. The indications for FEIBA were also extended to include prophylaxis in haemophilia A patients with high-responding inhibitors and frequent joint bleeding. The active ingredient for this product is human plasma proteins with factor VIII inhibitor bypassing activity. FEIBA 500 U powder and solvent for solution for infusion 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. This medicine is prescription only and may be administered to adults. 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.

FEIBA 500 U & 1000 U powder and solvent for solution for infusion is indicated for use in the following instances:

- 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

Haemophilia is a hereditary bleeding disorder, in which there is a partial or total lack of an essential blood clotting factor. It is a lifelong disorder, that results in excessive bleeding, and many times spontaneous bleeding, which, very often, is internal. Haemophilia A is the most common form, referred to as classical haemophilia. It is the result of a deficiency in clotting factor VIII, while haemophilia B (Christmas Disease) is a deficiency in clotting factor IX. This illness is a sex-linked recessive disorder. The two conditions have identical clinical features, which are managed with clotting factor replacement therapy.

A small proportion of patients with Haemophilia A develop factor VIII inhibitors following administration of factor VIII products to treat acute bleeding episodes. A similar situation may arise in haemophilia B with the development of factor IX inhibitors. The development of inhibitors represents one of the major clinical challenges in the management of haemophilia since bleeding episodes no longer respond to treatment with the relevant coagulation factor.

FEIBA (Factor Eight Inhibitor Bypassing Activity) is a pooled human plasma derivative. It is indicated in the UK for the control of bleeding episodes in Haemophilia A patients with factor VIII inhibitors or in patients with acquired factor VIII inhibitors. It has been clinically available since 1975, a vapour-heated formulation was introduced in 1985 in response to the need to avoid the potential transmission of blood borne viruses such as HIV.

Other treatments available in the United Kingdom for the treatment of bleeding in congenital Haemophilia A patients with factor VIII inhibitors include human factor VIII concentrate, desmopressin and recombinant factor VII (Novoseven).

The clinical and quality data presented to the MHRA in support of this variation application demonstrated that FEIBA 500 U & 1000 U powder and solvent for solution for infusion is effective for use in prophylaxis in haemophilia A patients with high-responding inhibitors and frequent joint bleeding. There were no unexpected safety concerns. It was therefore judged that the variation for extension of indication to include prophylaxis for FEIBA 500 U & 1000 U powder and solvent for solution for infusion, and to update the datasheet to an SPC could be granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, the UK granted a variation application for the medicinal product FEIBA 500 U & 1000 U powder and solvent for solution for infusion, (PL 00215/0021), which is a blood coagulation factor, on the 14th September 2007. The product is prescription only and may be administered to adults. 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.

This was a complex type II national variation application for FEIBA 500 U & 1000 U powder and solvent for solution for infusion to update the datasheet to an SPC to comply with current guidelines. In the process of this variation, a new indication was added for prophylaxis in haemophilia A patients.

FEIBA 500 U & 1000 U powder and solvent for solution for infusion is indicated for use in the following instances:

- 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

FEIBA 500 U & 1000 U powder and solvent for solution for infusion should be administered via the intravenous route following reconstitution. It should be injected slowly and the rate of administration should ensure the comfort of the patient and not exceed a maximum of 2 U/kg bw per minute.

The clinical and quality data presented to the MHRA in support of this variation application demonstrated that FEIBA 500 U & 1000 U powder and solvent for solution for infusion is effective for use in prophylaxis in haemophilia A patients with high-responding inhibitors and frequent joint bleeding. There were no unexpected safety concerns.

QUALITY ASSESSMENT

RECOMMENDATION

Based on a review of the data on quality, variation application 51 for PL 00215/0021 FEIBA 500 U & 1000 U powder and solvent for solution for infusion, to convert the product datasheet into an SPC was approvable.

EXECUTIVE SUMMARY

This was a type II variation to convert a datasheet to an SPC. A PIL, in line with the new SPC, was also been submitted.

SCIENTIFIC DISCUSSION

The pharmaceutical sections of the proposed SPC were checked against the original datasheet and the current licence for this product. Following a series of requests for further information modifications were made to the SPC and PIL in accordance with National and European requirements.

OVERALL CONCLUSION

This variation may be granted as the MA holder has provided satisfactory answers to the requests for supplementary information.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

EXECUTIVE SUMMARY

The MAH submitted a type II national complex variation to update the datasheet for FEIBA 500 U & 1000 U powder and solvent for solution for infusion to an SPC to comply with current guidelines on the 24th May 2005. In addition, the MAH proposed a new indication for prophylaxis in haemophilia A patients with high-responding inhibitors and frequent joint bleeding. This variation was approved, following the submission of additional data.

In the process of changing the data sheet format to an SPC format, extensive modifications were made to sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9 and 5.1 as detailed below.

The company submitted the following data to address a number of issues raised in a series of requests for further information.

- Efficacy
  - published literature and posters
  - Guideline from the UK Haemophilia Centre Doctors Organisation (UKHCDO) for the management of factors VIII & IX inhibitors
- Clinical safety:
  - Pharmacovigilance line listing of all cases received as of 31 Aug 2006
- Viral safety with regard to the non-enveloped virus HAV:
  - Risk Assessment Report dated 11 Sept 2006
- Clinical Overview
- Risk Management Plan
- New SPC proposal including the changes requested by the Assessor

SCIENTIFIC DISCUSSION OF CHANGES TO THE SPC

Section 4.1 Therapeutic indications

The MAH proposed a new indication for prophylaxis for FEIBA in section 4.1 of the SPC as part of this variation application. This indication has already been approved in eleven countries in the European Union including France, Belgium, Holland, Austria and Germany.

A restricted selection of published data was originally provided along with the recently published Guideline from the UK Haemophilia Centre Doctors Organisation (UKHCDO) for the management of factors VIII & IX inhibitors (Hay, 2006). This Guideline contains an assessment of current data available in prophylaxis.

*"**Prophylaxis**. The short half-life of factor VIII (FVIII), recombinant factor VIIa (rVIIa) and FEIBA in inhibitor patients have limited their usefulness as secondary prophylaxis. The longer half-life of thrombin generation observed with FEIBA when compared with rVIIa suggests that FEIBA may be the more useful prophylactic agent. Indeed, Hilgartner et al (2003) demonstrated limited efficacy of FEIBA 50-100 U/kg three times weekly in reducing the rate of joint bleeding in 4 of 6 patients and the rate of joint deterioration in 7 of 16 joints. Kreuz et al (2000) found that a more aggressive regimen of FEIBA 50-100 U/kg twice daily arrested joint deterioration and largely prevented bleeding in 5 patients. In contrast, Brackmann et al (2000) found that rVIIa 90 μg/kg b.d. did not influence the frequency of haemarthroses in five patients whereas a regimen of regular PCCs reduced the rate of bleeding by 50% in a further four. Two recent case reports of prophylaxis using rVIIa in the very high dose of 200 μg/kg 6 to 12-hourly (Young et al, 2005), show rVIIa may be used for prophylaxis if given in high enough dose. These reports suggest that if bypass agents are used in large enough doses and are given sufficiently frequently, they may have a useful prophylactic effect, but at very considerable cost. Further studies are planned."*

Subsequently, the MAH submitted a clinical overview to address the issue of prophylaxis and use in children, especially under 6 years; they conducted a literature review beyond 10 years to extend over the whole period within which FEIBA has been available for use within the United Kingdom i.e. 30 years.

Six independent case series of regular prophylaxis were found, including a total of 46 patients. The majority of these patients were children. A further 17 cases were identified through a post marketing surveillance study in the USA.

In addition, information about the ProFEIBA study conducted in the US was provided. This is a prospective, randomised, cross-over study of FEIBA for prophylaxis in patients with Haemophilia A and inhibitors. The study will treat 42 patients for a total of 15 months, with a randomised assignment to on demand therapy for 6 months followed by prophylaxis for 6 months after a 3 month wash out or vice versa. The dose of FEIBA administered during the prophylaxis period will initially be 85 U/kg three times weekly and then titrated according to clinical need. The study commenced in late 2003 and during the first three years, a total of 18 patients, 30% of the total planned, had been recruited (verbal communication Oct 2006). It therefore seems unlikely that the results of this study will be available within the next 6 or 7 years.

Evaluation of data

a) Regular prophylaxis indication

After careful review of the publications submitted by the MAH and taking into account duplicate reports for several patients, it appears that a limited amount of data is available. As pointed out by the MAH, the majority of prophylactic use is in children and adolescents.

Children/adolescents
Overall, 55 patients could be identified with either individual or collective data; 37 were less than 6 years old and 18 were aged 6 to 16 years. They were all patients with high-responding inhibitors. A number had failed immune tolerance induction (ITI) or were unsuitable for ITI while others were treated prophylactically during ITI. The dose was either adapted to the patient's bleeding tendency or fixed; it generally ranged from 50 to 100 U per kg bodyweight every other day (three times weekly) up to twice daily. When used to cover ITI in Germany, the patients in the first series received a high dose of 100 to 200 U/kg per day in two doses 12 hours apart whereas in the subsequent series the dose was reduced to 50 U/kg daily. The duration of the treatment ranged from 1.5 to 156 months, usually around 2-3 years; when administered to cover ITI, FEIBA was discontinued when inhibitor titres declined to 2 BU or less.

Adults
Only 6 individual cases of prophylaxis in adults were identified with seemingly extensive treatment durations. The dose ranged from 23 to 100 UI/kg daily or every other day (three times daily).

In addition, a retrospective post-licensure survey conducted by the MAH in the US and Europe mentioned 14 patients on prophylaxis, 4 children under 12 years and 10 patients over 12 years of age.

Efficacy and safety
In most cases, a decrease in the incidence of bleeding episodes was reported. Furthermore, radiologic and/or orthopaedic joint evaluation usually revealed no change or minor osteoathropathic alteration. However, mixed results were reported in a well-documented full publication; only two out of 7 patients experienced a clear decrease in the number of bleeding episodes and a functional improvement in their arthropathy. It was noted that arthropathy did not occur in the joints where bleeding had not previously occurred but new target joints developed in four patients when there was a previous history of bleeding into these joints. Overall, some level of improvement was also observed in the gait of three patients and in two patients who were in a wheelchair at the beginning of the prophylaxis. Finally, a dramatic reduction in the number of days absent from work was seen in one adult patient.

When data on inhibitor titres were presented, a fall was usually observed over the course of prophylaxis. However, anamnesis caused by FEIBA alone was reported in one patient after initiation of therapy with subsequent gradual decrease and no apparent impact on efficacy. The induction of an anamnestic response with a median increase in inhibitor level of 25 BU was also reported in 5/11 patients after exclusive exposure to FEIBA before onset of ITI therapy in another series.

A decrease in fibrinogen level (<0.9 g/L) and platelet count (<110,000/µL) was observed in two patients while a decrease in fibrinogen was reported in an additional patient.

b) Other data in children

A limited amount of data is available regarding treatment of acute bleeding episodes or to cover surgical interventions. They relate to 19 children and adolescents, including nine patients less than 6 years old and ten patients aged 6 – 16 years. The doses administered were similar to those used in adults, i.e. 40 to 100 U/kg per infusion at various intervals up to 6 hours.

In addition, in the retrospective post-licensure survey conducted by the MAH in the US and Europe the use of FEIBA in children as young as 1 year old has been mentioned.

Conclusions

Prophylaxis

As shown in recent publications, the consensus amongst experts from the UK Haemophilia Centre Doctors Organisation (Hay, 2006), the European Haemophilia Therapy Standardisation Board (Astermark, 2007), and the International Consensus Conference on Inhibitor Treatment in Haemophilia held in March 2006 in Cambridge, US (Berntorp, 2006) is that data are currently insufficient to make recommendations in regard to routine prophylaxis. Results from both the ProFEIBA and the NovoSeven prophylaxis trials are awaited with great interest in order to evaluate the effectiveness and safety of prophylactic therapy compared with on-demand therapy.

However, these experts also acknowledged that prophylaxis should be considered in patients with frequent joint bleeding, especially if they have failed ITI. Indeed, limited data available suggest that prophylaxis should be instituted early before significant joint damage has occurred; this means that the target population is mainly children, as seen in the literature review. In addition, data available do not suggest any unknown safety concern.

Due to the rarity of the condition and the difficulty to conduct a large controlled trial, it is acceptable to include a restricted prophylactic indication while waiting for the results of the ProFEIBA study, which should be submitted as soon as available; this wording should differentiate between regular prophylaxis and prevention of bleeding during and after surgical interventions. It was recommended that dosing in this latter indication should be expanded in the SPC: after the initial infusions up to 6-hourly, subsequent infusions should be given 8-12 hourly until wound healing.

Use in children less than 6 years

Although limited, available data indicate that the same posology as in adults can be used. This information was added to the SPC.

Other changes to the SPC

Extensive textual changes were also made to Sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9 and 5.1 of the SPC. These were all considered approvable following various modifications.

RISK MANAGEMENT PLAN

This is a European Risk Management Plan that was requested by some member states for the introduction on the market of FEIBA NF VH, the product manufactured with an additional step of nanofiltration.

Safety Specification

FEIBA was first marketed in 1977. The pivotal studies investigating efficacy and safety were 3 randomised controlled studies and one retrospective multicentre study. Since then a long term follow up study and a survey of FEIBA use have also added to the knowledge of the safety profile of this product.

Data on prophylactic use in 55 children and adolescents, and 6 adults has been collated from a number of published papers.

The estimated post marketing usage of this product is 688,942 “on-demand” treatments, based on manufacturing data.

During the period 01/02/1994 – 31/01/2007 a total of 121 adverse reaction reports have been received. 75 of these were classified as serious. No reports have been received from patients using the new generation product FEIBA NF VH, since its launch in June 2006.

Two types of known adverse events have been identified as risks with FEIBA. These are allergic-type sensitivity reactions, and disseminated intravascular coagulation (DIC). Additionally best demonstrated practices for the prophylactic use of FEIBA in haemophilia A patients with inhibitors is not well defined due to the rarity of the condition. The generation of additional safety and efficacy data to enhance the development of clinical best practice would facilitate improved treatment of this group of patients.

Pharmacovigilance Plan

In addition to routine pharmacovigilance the company plan to conduct a Post-Authorization Safety Surveillance (PASS) study (PASS-EU-006), for which the draft protocol has been provided.

PASS-EU-006

This is an open uncontrolled non-interventional observational cohort study of FEIBA NF in haemophiliacs with inhibitors, for treatment or prophylaxis of bleeding, designed to investigate general safety and tolerance, haemostatic efficacy and identify best practice in managing these patients.

The study plans to enrol at least 15 patients. Subjects will be followed up for 6 months after enrolment in the study.

UK specific study extension proposal

The UK additionally requested that a specific surveillance of patients following a prophylaxis regimen be completed. To address this request the company have submitted an extension plan for the PASS-EU-006 study. This extension proposal sets out a planned 3 year follow-up of all patients who had been recruited to the PASS-EU-006 study after their 6 month follow-up as outlined in the original protocol.

Timelines:
Recruitment to the European FEIBA NF PASS surveillance will commence in Q1 2008, subject to National and Local ethics approvals.
Subsequent extension of the surveillance will occur to follow patients for a total of 3 years, with recruitment thus closing at end of 2009.
Last patient last visit will thus be end of 2012.

Reporting
Regular update of this study will be submitted to the MHRA. These will include an interim report when the first 7 patients have completed their 6 month follow up, a final report when all 15 patients have completed the 6 month follow-up, and a final report when all UK patients have completed the full follow up.

Risk minimisation Plan

The company plans no additional risk minimisation activities.

Conclusions

Following amendments requested by the Assessors, the Risk Management Plan for FEIBA was considered acceptable.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of FEIBA are well defined and controlled. No new quality data were submitted and there are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

CLINICAL

Published clinical data were submitted to support an extension of indication. No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the variation application on 24th May 2005.
2	The MHRA's assessment of the submitted data was completed on 3rd October 2005.
3	Following assessment, a request for supplementary information was sent to the applicant in a letter dated 3rd October 2005 regarding the SPC and PIL content.
4	The applicant submitted its response to the supplementary information request which was received 29th August 2006.
5	A further request for supplementary information was sent to the applicant in a letter dated 8th September 2006 with regard to outstanding issues relating to the content of the SPC and PIL.
6	The applicant submitted its responses to the supplementary information request which was received 1st November 2006.
7	A further request for supplementary information was sent to the applicant in a letter dated 20th December 2006 with regard to outstanding issues relating to extension of indication, clinical overview and further amendments to clinical parts of the SPC.
8	The applicant submitted its responses to supplementary information request which was received 16th February 2007.
9	Following assessment, a request for supplementary information was sent to the applicant on 14th March 2007.
10	The application was submitted for consultation with a haematology expert who responded on 25th April 2007.
11	A response was received from the applicant on 25th April 2007 discussing the proposed changes to the SPC.
12	A further request for supplementary information was sent to the applicant in a letter dated 26th April 2007 regarding a restricted prophylactic indication, submission of a Risk Management Plan (RMP) and further amendments to the SPC and consequently the PIL.
13	The applicant submitted an RMP, an updated PIL and an updated proposed SPC in response to the previous request for supplementary information on 21st June 2007.
14	A request for supplementary information was sent to the applicant in a letter dated 28th June 2007 with regard to amendments to the SPC, PIL and RMP.
15	The applicant submitted its responses regarding the SPC, PIL, and RMP on 25th July 2007.
16	A request for further information regarding the PIL was sent to the applicant on 7th August 2007.

17	The applicant responded to the previous request for further information regarding the PIL on 22nd August 2007 and submitted revised versions of the SPC and PIL.
18	A request for supplementary information regarding the Risk Management Plan (RMP) was sent to the applicant in a letter dated 13th August 2007.
19	The applicant submitted its responses to supplementary information request regarding the UK specific study extension proposal and the RMP on 22nd August 2007.
20	Requests for final mock-ups for labels and PIL were sent to the applicant on 29th August 2007.
21	The MHRA completed its assessment of the application on 29th August 2007.
22	The application was determined on 29th August 2007.
23	The applicant submitted the requested final mock-ups on 7th September 2007.
24	The MHRA granted the application on 14th September 2007.

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
12/07/2005	Type II Standard National Variation	To replace the Pyrogen test with the Bacterial Endotoxin Test.	Granted 18/11/2005
02/08/2006	Type II Standard National Variation	To supply 1 batch (VNF1A020) of FEIBA 500 U product with English language in USA labelling.	Granted 02/08/2006
12/10/2006	Type II Standard National Variation	To introduce a nanofiltration step to the manufacturing process of the drug substance in order to increase the safety margin of the drug product.	Granted 03/11/2006
06/11/2006	Type II Standard National Variation	To replace the preceding reference standard (5231R00) used in the determination of PKA with a new internal reference standard (5251R00), which is calibrated against the new WHO-standard (#02/168).To adjust the new reference standard (5251R00) according to the European Pharmacopoeia using a calibration curve with several conditions.	Granted 10/01/2007
12/12/2006	Type IB National Variation	To change the product name from FEIBA Immuno to FEIBA.	Granted 26/02/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FEIBA 500 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 200-600 mg human plasma protein with a Factor Eight Inhibitor Bypassing Activity of 500 U* per vial.

The final solution has an activity of approximately 25 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

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
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.

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.

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.

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

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 and 1 transfer 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.
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.

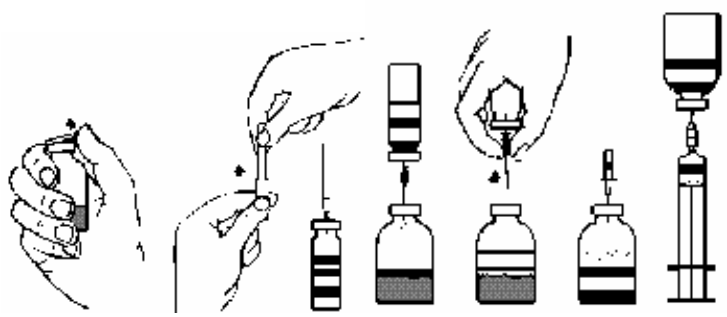


fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6 fig. 7

7 MARKETING AUTHORISATION HOLDER

Immuno Ltd
Caxton Way,
Thetford, Norfolk
IP24 3SE
United Kingdom

8 MARKETING AUTHORISATION NUMBERS

PL 0215/0021
Solvent PL 0215/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 1985

10 DATE OF REVISION OF THE TEXT

August 2007

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

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
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.

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.

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 increase 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.

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 administration of high doses of FEIBA. In such cases administration of the product should be stopped promptly (see also 4.4).

5. PHARMACOLOGICAL 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

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 and 1 transfer 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.

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.

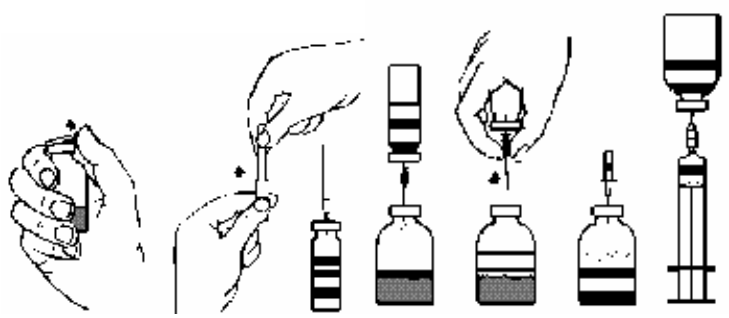


fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6 fig. 7

7. MARKETING AUTHORISATION HOLDER

Immuno Ltd
Caxton Way,
Thetford, Norfolk
IP24 3SE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00215/0022
Solvent PL 00215/0028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

17 October 1985

10 DATE OF REVISION OF THE TEXT

14/09/2007

Patient Information Leaflet

FEIBA 500 U & 1000 U POWDER AND SOLVENT FOR SOLUTION FOR INFUSION

(HUMAN PLASMA PROTEINS WITH FACTOR VIII INHIBITOR BYPASSING ACTIVITY)

PL 00215/0021-22

FEIBA

POWDER AND SOLVENT FOR SOLUTION FOR INFUSION

P.O.M.

Baxter

6205820EA12

CHARACTERISTICS AND COMPOSITION

FEIBA contains an anti-inhibitor coagulant complex with standardised FEIB-activity[1] (Factor Eight Inhibitor Bypassing Activity):

1 mg of protein contains 0.8 to 2.5 units FEIBA. FEIBA contains factor 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/I U FEIBA. The factors of the kallikrein-kinin system are present in trace amounts or absent.

FEIBA is prepared from pooled human venous plasma. The plasma donations are obtained from blood banks and licenced plasmapheresis centres in Europe and the United States of America, but not in the UK.

For the manufacture of FEIBA only plasma units are used which were ALT-tested and were non-reactive in tests for HBs- antigen and antibody to HIV-1, HIV-2, and HCV. The state of the art suggests that it cannot be precluded with certainty that both known or unknown viruses, which may occur in plasma, are transmitted through factor concentrates.

INDICATIONS

FEIBA is indicated for:

- the control of spontaneous bleeding episodes and cover of surgical interventions in Haemophilia A patients with factor VIII inhibitors and in patients with acquired factor VIII inhibitors
- the prophylaxis in Haemophilia A patients with high-responding inhibitors and frequent joint bleeding.

For guidelines for treatment of patients with inhibitors see Table 1

Table 1: Guidelines for Treatment of patients with inhibitors

Inhibitor titre (BU*/ml)	Response to FVIII treatment	Minor to moderate bleeding	Severe to life-threatening bleeding, surgery
<5	low responder high responder	F VIII or FEIBA FEIBA	F VIII or FEIBA FEIBA
5 – 10	low responder high responder	F VIII or FEIBA FEIBA	FEIBA FEIBA
>10	low responder high responder	FEIBA FEIBA	FEIBA FEIBA

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

DOSAGE AND ADMINISTRATION

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

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

Dosage is independent of the patient's inhibitor titre. Since the response to treatment may differ from patient to patient the dosage recommendations are only guidelines.

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 need not correlate with clinical improvement. For this reason these tests have only very limited value for monitoring FEIBA therapy.

[1] 1 unit FEIBA is defined as that amount of factor VIII inhibitor bypassing fraction human which shortened the activated partial thromboplastin time (APTT) of a F VIII inhibitor plasma to 50% of the buffer value (blank).

1. Spontaneous Haemorrhage

Joint, muscle and soft tissue haemorrhage

For minor to moderate bleeds a dose of 50 – 75 U/kg bodyweight is recommended at 12-hour intervals. Treatment should be continued until clear signs of clinical improvement appear, such as relief of pain, reduction of swelling or mobilisation of the joint.

For major muscle and soft tissue haemorrhage, such as retroperitoneal bleeding, doses of 100 U/kg bodyweight at 12 hour intervals are recommended.

Mucous membrane haemorrhage

A dose of 50 U/kg bodyweight is recommended to be given every 6 hours with careful monitoring of the patient (visible bleeding site, repeated measurements of haematocrit). Again if haemorrhage does not stop, the dose may be increased to 100 U/kg bodyweight taking care not to exceed the maximum daily dose of 200 U/kg bodyweight.

Other severe haemorrhage (e.g. CNS)

Severe haemorrhage, such as CNS bleeding has been effectively treated with doses of 100 U/kg bodyweight at 12 hour intervals. In individual cases FEIBA may be given at intervals of 6 hours until clear clinical improvement is achieved. (Do not exceed the maximum daily dose).

2. Surgery

Take care not to exceed the maximum daily dose; 50 – 100 U/kg body weight should be given at intervals of up to 6 hours, then every 8 – 12 hours until wound healing.

3. Bleeding prophylaxis

Posology should be adapted to the patient's bleeding tendency within the following dose range: 50 to 100 U/kg body weight from daily to three times a week. When administering during ITI, a daily dose of 50U/kg body weight may be sufficient.

Paediatric population:

The experience in children under 6 years is limited; the same dose regimen as in adults should be adapted to the child's clinical condition.

Use in pregnancy

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.

RECONSTITUTION OF CONCENTRATE

FEIBA is to be made up immediately before use only. The solution should then be used promptly. Any unused solution must be discarded appropriately.

Reconstitution of dried substance:

1. Warm the unopened vial containing solvent (Water for Injection B.P.) to room temperature (max. +37°C).
2. Remove protective caps from the concentrate vial and solvent vial (Fig. A) and disinfect the rubber stoppers of both.
3. Remove protective covering from one end of the enclosed "transfer needle" by twisting and pulling (Fig. B). Insert the exposed needle through the rubber stopper of the solvent vial (Fig. C).
4. Remove 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 concentrate vial, and insert the free end of the transfer needle through the rubber stopper of the concentrate vial (Fig. D). The solvent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing the needle from the concentrate vial (Fig. E). Gently agitate or rotate the concentrate vial to accelerate dissolution.
7. Upon complete reconstitution of the concentrate, insert the enclosed "aeration needle" (Fig. F) and any foam will collapse. Remove aeration needle.

Injection/Infusion:

1. Remove protective covering from the enclosed "filter needle" by twisting and pulling and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (Fig. G).
2. Disconnect the filter needle from the syringe and slowly inject the solution into a vein with a winged infusion set or disposable needle.

If administered by infusion, a disposable infusion set with adequate filter is to be used.

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

WARNINGS AND PRECAUTIONS

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.

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.

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 which 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.

SIDE EFFECTS:

The most frequent are 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.

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.

INTERACTIONS

It is not recommended to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA treatment. However, if treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA is indicated, the products should be administered at least 6 hours apart.

Treatment of Overdosage

Occasionally biological and/or clinical signs of DIC have been observed following the administration of high doses of FEIBA. In such cases administration of the product should be stopped promptly.

Effects on Laboratory tests

Inherent in its mechanism of action FEIBA causes a shortening of the following clotting times: activated partial thromboplastin time (APTT), whole blood clotting time (WBCT), activated clotting time (ACT), thromboelastogram (TEG).

Coagulation tests measuring the extrinsic coagulation system such as the prothrombin time, which is usually normal in haemophiliacs remained unchanged after treatment with FEIBA.

Overdosage of the product may result in laboratory signs of DIC such as the presence of fibrin/fibrinogen degradation products, a fall in fibrinogen, a decreased platelet count.

SHELF LIFE AND STORAGE

Two years when stored between +2°C and +8°C. Keep container in the outer carton in order to protect from light.

Within the indicated shelf life period the product may be stored at room temperature (maximum 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.

FEIBA must not be used beyond the expiry date indicated.

Keep out of the reach of children!

PACKS

FEIBA 500
- R/C vial containing 500 FEIBA-units, lyophilised
- R/C vial containing 20ml sterilised Water for Injections
- 1 transfer needle, 1 filter needle and 1 aeration needle

FEIBA 1000
- R/C vial containing 1000 FEIBA-units, lyophilised
- R/C vial containing 20ml sterilised Water for Injections
- 1 transfer needle, 1 filter needle and 1 aeration needle

Product Licence Holder
IMMUNO LTD,
Caxton Way, Thetford, Norfolk IP24 3SE
United Kingdom

Manufactured by
Baxter AG, Vienna, Austria

Date of Preparation
August 2007

PATIENT INFORMATION LEAFLET

FEIBA

POWDER AND SOLVENT FOR SOLUTION FOR INFUSION

P.O.M.

Baxter

6205820EA12

WHAT DOES FEIBA CONTAIN?

Active ingredient:

Human Plasma Protein with a Factor Eight Inhibitor Bypassing Activity of	200 – 600 mg	or	400 – 1200 mg
	500 units	or	1000 units

Other ingredients:

Sodium Chloride	160 mg	160 mg
Sodium Citrate	80 mg	80 mg

Other ingredient: protein

One vial of FEIBA contains 81.7 mg of sodium. This should be taken into consideration in people on a low sodium diet.

FEIBA contains factors II, IX and X mainly in non-activated form as well as activated factor VII; factor VIII coagulant antigen (F VIII C:Ag) is present in a concentration of up to 0.1 IU/ U FEIBA. Other factors naturally occurring in the blood may be present only in trace amounts.

HOW IS FEIBA SUPPLIED?

FEIBA is supplied as a dried substance together with a bottle of sterilised Water for Injections to make a solution.

FEIBA is available in sizes of 500 and 1000 units, to be dissolved in 20ml of sterilised Water for Injections. Each pack also includes a transfer needle, an aeriation needle and a filter needle.

HOW DOES FEIBA WORK?

FEIBA is a coagulation factor concentrate. It contains an anti-inhibitor coagulant complex with standardised Factor Eight Inhibitor Bypassing Activity for use in patients who have developed inhibitors (antibodies) to Factor VIII. Factor VIII is a component of the blood, essential for normal blood clotting processes and if you have inhibitors your blood will not clot properly.

LICENCE HOLDER

Immuno Ltd., Caxton Way, Thetford, Norfolk, IP24 3SE, United Kingdom

Product Licence No. 0215/0021-22

MANUFACTURER

Baxter AG, Vienna, Austria

WHO SHOULD RECEIVE FEIBA?

FEIBA is used for the treatment of spontaneous bleeding episodes and cover of surgery in Haemophilia A patients with inhibitors to their usual Factor VIII Concentrates.

In addition, FEIBA may be used for treating non-haemophiliacs who have developed inhibitors to factor VIII.

FEIBA is also used for prophylaxis (prevention) of bleeding in Haemophilia A patients with frequent joint bleeding.

WHEN SHOULD FEIBA NOT BE GIVEN?

FEIBA should not be given if you are suffering from:

1. Hypersensitivity (allergy) to the product
2. Disseminated Intravascular Coagulation (DIC) - an excessive activation of the blood clotting system

   NOTE: DIC usually occurs in connection with severe disease, injury, or a major operation and will be diagnosed by your doctor using laboratory tests.
3. Liver damage, because of risk of DIC, except if no other treatment is susceptible to work
4. Heart attack, severe clot formations or clots in the lung (embolism), except in case of life threatening bleeding episodes.

PRECAUTIONS WHEN TAKING FEIBA

Please see side effects.

SIGNIFICANCE OF PLATELET COUNT

If there is an inadequate or reduced response to treatment with FEIBA your doctor may carry out a platelet count, since a sufficient number of functionally intact platelets is considered necessary for FEIBA to work.

DO OTHER MEDICINES AFFECT THE ACTION OF FEIBA?

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

If treatment with drugs such as epsilon-aminocaproic acid and FEIBA is to be carried out, the time interval between the giving of either product should be at least 6 hours.

IS FEIBA SAFE TO USE WHEN YOU ARE PREGNANT OR BREAST FEEDING?

The safety of FEIBA for use in human pregnancy or breastfeeding has not be established.

Because of the increased risk of clotting during pregnancy FEIBA should only be used if no alternative treatment is available.

FEIBA should not been used during breast feeding.

SPECIAL WARNINGS

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 that 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 infection.

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 viruses such as hepatitis A virus. However, the measures taken may be of limited value against parvovirus B19; parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

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.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly receive human blood-derived products.

(Further information is provided at the end of this leaflet).

HOW MUCH FEIBA DO YOU NEED

This product is for intravenous infusion. As a general guide a dose of 50 to 100 units of FEIBA per kg body weight (b.w.) is recommended, however, not exceeding a single dose of 100 U/kg and a daily dose of 200 U/kg b.w.

Your doctor will tell you how often and at what intervals FEIBA is to be administered.

WHAT HAPPENS IF YOU RECEIVE TOO MUCH FEIBA?

Occasionally laboratory tests and symptoms indicating DIC have been observed following the use of high doses of FEIBA.

In such cases your treatment should be stopped quickly and your doctor will take further actions as appropriate.

HOW TO DISSOLVE AND INJECT FEIBA

FEIBA is to be made up immediately before use only.

The solution should then be used promptly.

Any unused solution must be discarded appropriately.

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.

Reconstitution of dried substance:

1. Warm the unopened vial containing solvent (Water for Injection B.P.) to room temperature (max. +37°C).
2. Remove protective caps from the concentrate vial and solvent vial (Fig. A) and disinfect the rubber stoppers of both.
3. Remove protective covering from one end of the enclosed "transfer needle" by twisting and pulling (Fig. B). Insert the exposed needle through the rubber stopper of the solvent vial (Fig. C).
4. Remove 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 concentrate vial, and insert the free end of the transfer needle through the rubber stopper of the concentrate vial (Fig. D). The solvent will be drawn into the concentrate vial by vacuum.
6. Disconnect the two vials by removing the needle from the concentrate vial (Fig. E). Gently agitate or rotate the concentrate vial to accelerate dissolution.
7. Upon complete reconstitution of the concentrate, insert the enclosed "aeration needle" (Fig. F) and any foam will collapse. Remove aeration needle.

Injection/Infusion:

1. Remove protective covering from the enclosed "filter needle" by twisting and pulling and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (Fig. G).
2. Disconnect the filter needle from the syringe and slowly inject the solution into a vein with a winged infusion set or the disposable needle.

If administered by infusion, a disposable infusion set with adequate filter is to be used.

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

MONITORING OF THERAPY

Single doses of 100 units FEIBA per kg bodyweight and daily doses of 200 units FEIBA per kg body weight should not be exceeded. Patients given single doses of 100 units FEIBA per kg body weight 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.

Should changes in blood pressure, pulse rate, breathing problems, chest pain or cough occur, the infusion should be stopped immediately and appropriate medical tests carried out.

SIDE EFFECTS

Rapid intravenous injection or infusion (exceeding 2 U per kg body weight per minute) may cause pain at the injection site and numbness in the face and extremities as well as a drop in blood pressure.

If minor allergic reactions such as rashes, fever or nausea occur during the administration of FEIBA, the infusion should be stopped and your doctor will prescribe anti-histamines.

In the rare case of severe hypersensitivity reactions your doctor will follow the current guidelines of shock treatment.

If you have experienced allergic reactions to plasma derivatives in the past then your doctor may prescribe anti-histamines as a preventative measure.

After administration of high doses (single doses of 100 units FEIBA per kg bodyweight and daily doses of 200 units per kg bodyweight) excessive activation of the blood clotting system (Disseminated Intravascular Coagulation) was observed in a few cases.

In very rare cases myocardial infarction (heart attack) occurred after high doses and/or prolonged administration in the presence of risk factors predisposing to cardiovascular disease.

Blood clots in the circulation and lungs have been reported.

Please tell your doctor or pharmacist of any suspected undesirable effect that is not mentioned in this leaflet.

SHELF LIFE AND STORAGE

FEIBA is stable for two years when stored between +2°C and +8°C. Keep container in the outer container in order to protect from light.

Within the shelf life the product may be stored at room temperature (max. 25°C) for a period of up to 6 months. The dates between which the product is not stored at refrigerator temperature should be noted on the package. Do not return to the fridge following storage at room temperature.

FEIBA must not be used beyond the expiry date printed on the label.

Store out of the reach of children.

Date of revision August 2007.

FURTHER INFORMATION

Only plasma from healthy donors which has been tested with negative results for antibodies to human immunodeficiency virus types 1 and 2 (HIV-1 and -2) and hepatitis C virus (HCV) as well as hepatitis B virus surface antigen (HBsAg) is used for the manufacture of FEIBA. The liver enzyme value (ALT) must not exceed the accepted threshold value (twice the upper limit of normal). Further measures include Non-Returning Donor-Applicant Exclusion, Inventory Hold for each plasma donation (minimum three months) and the Lookback Program.

Each plasma pool is tested for HIV and HCV antibodies as well as for HBsAg. In addition a test for virus genome sequences of HIV-1, HBV and HCV with the polymerase chain reaction (IQ-PCR[1]) is carried out. The polymerase chain reaction (PCR) is a highly sensitive method with which, in contrast to antibody testing, direct identification of virus genomes is possible. Only plasma pools in which no genomes of these viruses are detectable are released for further processing.

In prospective international safety studies with coagulation factor concentrates virus inactivated by vapour heat treatment, none of the patients, who were all previously untreated, showed any evidence of a transmission of hepatitis viruses or HIV. Pharmaco-epidemiological surveillance of FEIBA has shown no product-related transmission of the above mentioned agents.

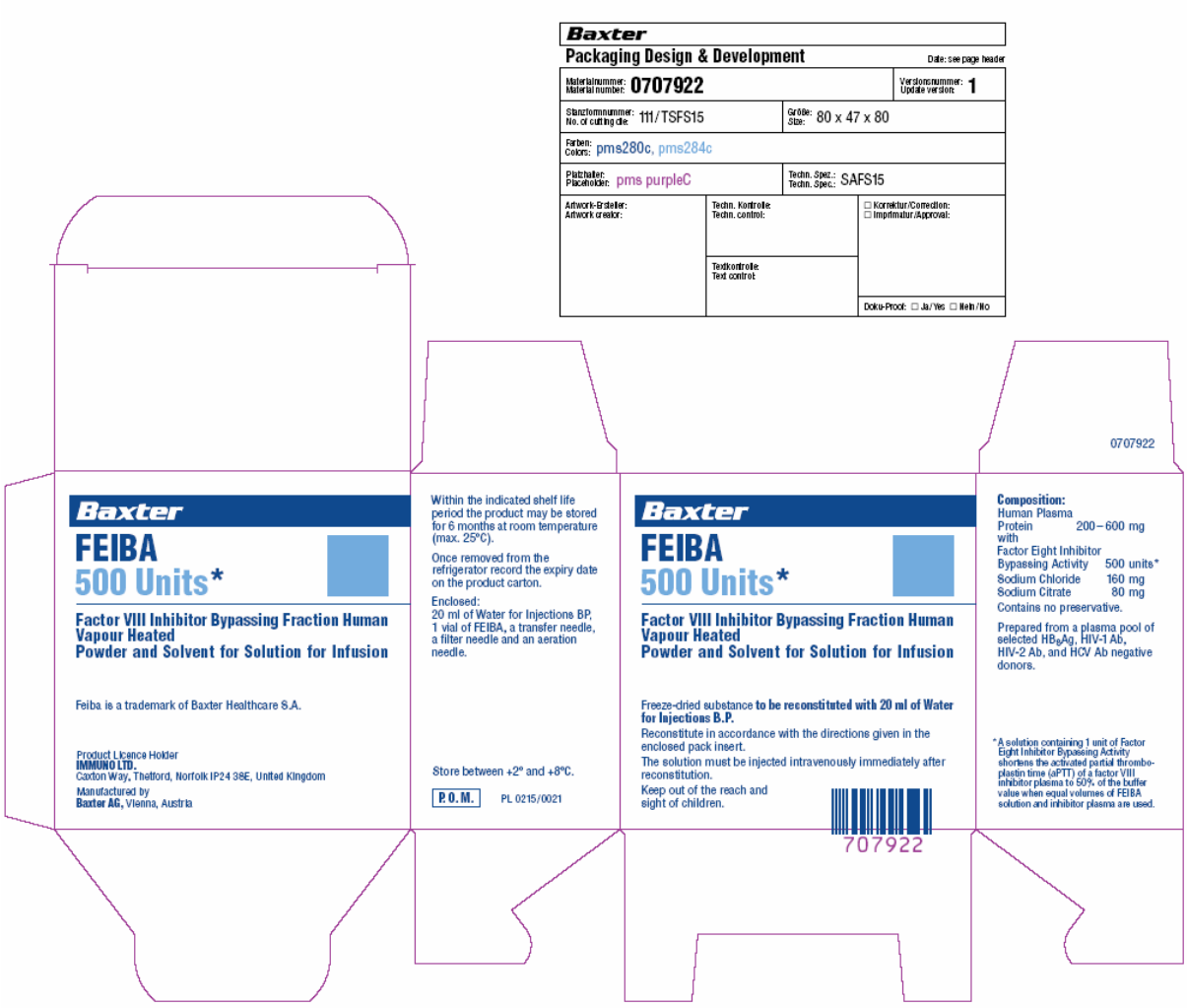
[1] HIQ-PCR (Hyland Immuno Quality-Assured Polymerase Chain Reaction) is a quality-assured assay system for the detection of genomic sequences of HIV-1, HBV, and HCV. With the highest degree of probability this assay system allows for the detection of 500 genome equivalents of each of the above viruses per ml, its sensitivity being below this limit. Also test results ranging below 500 genome equivalents per ml are considered positive leading to exclusion of the respective donation from further processing.

Labelling

FEIBA 500 U & 1000 U POWDER AND SOLVENT FOR SOLUTION FOR INFUSION

(HUMAN PLASMA PROTEINS WITH FACTOR VIII INHIBITOR BYPASSING ACTIVITY)

PL 00215/0021-22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0707922
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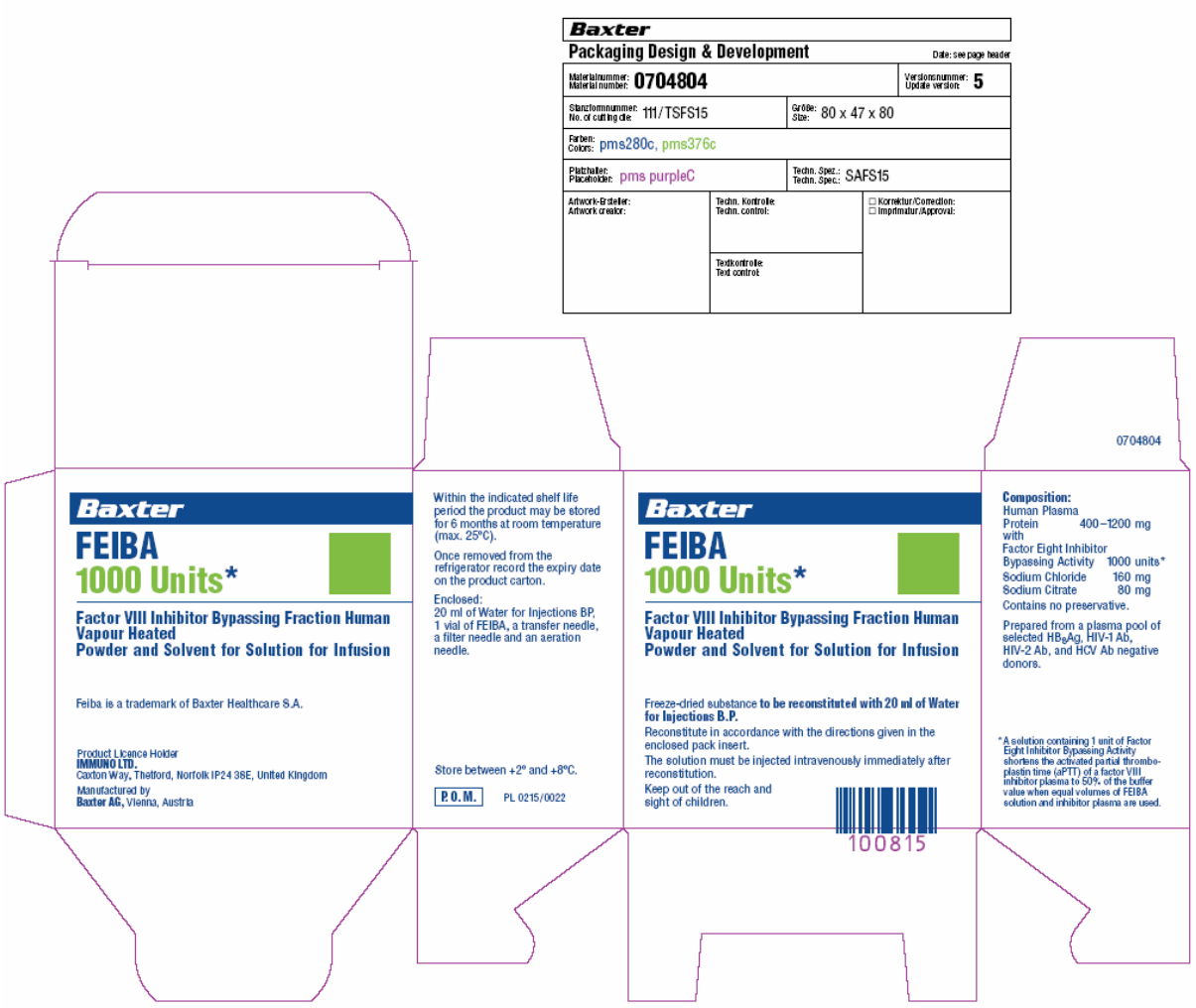
FEIBA
500 Units*
Factor VIII Inhibitor Bypassing Fraction Human Vapour Heated
Powder and Solvent for Solution for Infusion
Feiba is a trademark of Baxter Healthcare S.A.
Product Licence Holder
IMMUNO LTD.
Caxton Way, Thetford, Norfolk IP24 3SE, United Kingdom
Manufactured by
Baxter AG, Vienna, Austria
Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 25°C).
Once removed from the refrigerator record the expiry date on the product carton.
Enclosed:
20 ml of Water for Injections BP,
1 vial of FEIBA, a transfer needle, a filter needle and an aeration needle.
Store between +2° and +8°C.
P.O.M.
PL 0215/0021
Baxter
FEIBA
500 Units*
Factor VIII Inhibitor Bypassing Fraction Human Vapour Heated
Powder and Solvent for Solution for Infusion
Freeze-dried substance to be reconstituted with 20 ml of Water for Injections B.P.
Reconstitute in accordance with the directions given in the enclosed pack insert.
The solution must be injected intravenously immediately after reconstitution.
Keep out of the reach and sight of children.
707922
Composition:
Human Plasma
Protein 200 – 600 mg
with
Factor Eight Inhibitor
Bypassing Activity 500 units*
Sodium Chloride 160 mg
Sodium Citrate 80 mg
Contains no preservative.
Prepared from a plasma pool of selected HBsAg, HIV-1 Ab, HIV-2 Ab, and HCV Ab negative donors.
*A solution containing 1 unit of Factor Eight Inhibitor Bypassing Activity shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma to 50% of the buffer value when equal volumes of FEIBA solution and inhibitor plasma are used.



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FEIBA
1000 Units*

Factor VIII Inhibitor Bypassing Fraction Human
Vapour Heated
Powder and Solvent for Solution for Infusion

Feiba is a trademark of Baxter Healthcare S.A.

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IMMUNO LTD.
Caxton Way, Thetford, Norfolk IP24 3SE, United Kingdom
Manufactured by
Baxter AG, Vienna, Austria

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 25°C).

Once removed from the refrigerator record the expiry date on the product carton.

Enclosed:
20 ml of Water for Injections BP,
1 vial of FEIBA, a transfer needle, a filter needle and an aeration needle.

Store between +2° and +8°C.

P.O.M. PL 0215/0022

Baxter

FEIBA
1000 Units*

Factor VIII Inhibitor Bypassing Fraction Human
Vapour Heated
Powder and Solvent for Solution for Infusion

Freeze-dried substance **to be reconstituted with 20 ml of Water for Injections B.P.**
Reconstitute in accordance with the directions given in the enclosed pack insert.
The solution must be injected intravenously immediately after reconstitution.
Keep out of the reach and sight of children.

100815

Composition:
Human Plasma Protein 400–1200 mg
with
Factor Eight Inhibitor Bypassing Activity 1000 units*
Sodium Chloride 160 mg
Sodium Citrate 80 mg
Contains no preservative.

Prepared from a plasma pool of selected HB_sAg, HIV-1 Ab, HIV-2 Ab, and HCV Ab negative donors.

*A solution containing 1 unit of Factor Eight Inhibitor Bypassing Activity shortens the activated partial thromboplastin time (aPTT) of a factor VIII inhibitor plasma to 50% of the buffer value when equal volumes of FEIBA solution and inhibitor plasma are used.

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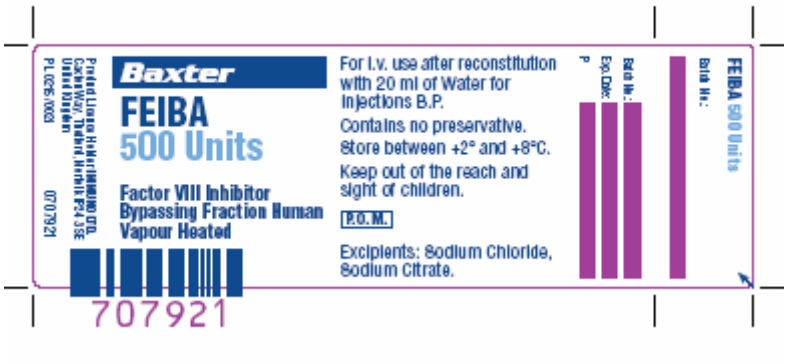

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