

PRODUCT MONOGRAPH

FEIBA VH IMMUNO

Anti-Inhibitor Coagulant Complex, Vapor Heated,
Freeze-Dried Substance With Solvent for
Intravenous Injection or Infusion

Human Plasma Fraction with Factor VIII Inhibitor Bypassing Activity

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ACTION AND CLINICAL PHARMACOLOGY

In a preclinical study to determine the virus inactivating efficacy of vapor heating, samples of bulk Anti-Inhibitor Coagulant Complex, Vapor Heated FEIBA VH IMMUNO were spiked with 2×10^6 /mL infectious units of HIV and subjected to vapor heat treatment. The residual virus titer was found to be less than 1 infectious unit/0.5 ml. A clinical study⁴ testing Antihemophilic Factor treated by a similar vapor heating procedure has shown none of 4 lots used in the study to produce nonA, nonB hepatitis in intensively followed patients naïve to blood product administration.

The safety and efficacy of FEIBA VH IMMUNO has been demonstrated by two prospective clinical trials⁵⁻⁷. The first, conducted by Sixma and collaborators during 1979 and early 1980, was a randomized double-blind study comparing the effect of FEIBA VH IMMUNO and PROTHROMPLEX IMMUNO (a non-activated prothrombin complex concentrate) in 15 patients with hemophilia A and inhibitors to Factor VIII. A total of 150 bleeding episodes (primarily joint and musculoskeletal plus a few mucocutaneous) were treated. A single dose of 88 IMMUNO Units per kg of body weight was used uniformly for treatments with FEIBA VH IMMUNO. The study showed that, based on subjective patient evaluation, FEIBA IMMUNO was fully effective in 41.0% and partly effective in 24.6% of episodes (i.e. combined effectiveness of 65.6%), while PROTHROMPLEX IMMUNO was rated fully effective in 25.0% and partly effective in 21.4% of episodes (i.e. combined effectiveness of 46.4%).

The second study with FEIBA VH IMMUNO was a multiclinic study conducted by Hilgartner *et al.* It was designed to evaluate the efficacy of FEIBA VH IMMUNO in the treatment of joint, mucous membrane, musculoskeletal and emergency bleeding episodes such as central nervous system hemorrhages and surgical bleedings. In 49 patients with inhibitor titres of greater than 5 Bethesda Units (from nine cooperating hemophilia centers), 489 single doses were given for the treatment of 165 bleeding episodes. The usual dosage was 50 IMMUNO Units per kg of body weight, repeated at 12-hour intervals (6-hour intervals in mucous membrane bleedings), if necessary. Bleeding was controlled in 153 episodes (93%). In 130 (78%) of the episodes hemostasis was achieved with one or more infusions within 36 hours. Of these, 36% were controlled with one infusion within 12 hours. An additional 14% of episodes responded after more than 36 hours.

Of the 489 single doses only 18 (3.7%) caused minor transient reactions in recipients. 10 out of 49 patients (20%) showed a rise in their inhibitor titers. In 5 of these patients (10%) the rise was tenfold or more. However, of these 10 patients 3 had received Factor VIII or Factor IX concentrates within 2 weeks prior to treatment with FEIBA VH IMMUNO. These anamnestic rises have not been observed to interfere with the efficacy of Anti-Inhibitor Coagulant Complex, FEIBA VH IMMUNO.

INDICATIONS AND CLINICAL USE

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO is indicated for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and B patients with inhibitors.

In addition, FEIBA VH IMMUNO may be used for treating non-haemophiliacs with acquired inhibitors to factors VIII, XI and XII in case of life-threatening haemorrhages⁵⁻¹². One case has been reported where FEIBA VH IMMUNO was effective in a patient with von Willebrand's disease with an inhibitor¹⁶.

Clinical experience suggests that patients with a Factor VIII inhibitor titer of less than 5 B.U. may be successfully treated with Antihemophilic Factor. Patients with titers ranging between 5 and 10 B.U. may either be treated with Antihemophilic Factor or FEIBA VH IMMUNO. Cases with Factor VIII inhibitor titers greater than 10 B.U. have generally been refractory to treatment with Antihemophilic Factor.

Guidelines to First and Second Choice Treatment:

AICC = Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO

AHF = Antihemophilic Factor

Patient's Inhibitor Titer	Clinical Situation		
	Minor Bleeding	Major Bleeding	Surgery (Emergency)
less than 5 B.U.	AHF	AHF	AHF
5 to 10 B.U.	AHF AICC	AHF AICC	AHF AICC
more than 10 B.U.	AICC	AICC	AICC

Inadequate response to treatment may result from an abnormal platelet count or impaired platelet function¹³⁻¹⁵ which were present before treatment with FEIBA VH IMMUNO.

CONTRAINDICATIONS

The use of Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO is contraindicated in patients who are known to have a normal coagulation mechanism.

It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis. In patients with a tentative or definite diagnosis of coronary heart disease as well as in patients with acute thrombosis and/or embolism the use of FEIBA VH IMMUNO is only indicated in life-threatening bleeding events.

WARNINGS

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO must be used only in patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies. It should not be given to patients with significant signs of disseminated intravascular coagulation (DIC) or fibrinolysis.

This product is manufactured using components of human blood which may contain the causative agents of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized at the plasma collection centres and plasma testing laboratories are designed to reduce the risk of transmitting viral infection. However, the risk of the transmission of infective agents - also of hitherto unknown origin - cannot be totally eliminated.

In rare instances myocardial infarction, pulmonary embolism or thrombosis may occur after high doses and/or prolonged administration of FEIBA VH IMMUNO. This is particularly the case in patients with risk factors predisposing to myocardial infarction or thrombosis (e.g. patients in the postoperative state or with liver disease, infection, inflammation, cancer, angina pectoris or myocardial infarction).

Anamnestic response with rise in Factor VIII inhibitor titer have been observed in 20% of the cases (see CLINICAL PHARMACOLOGY) .

PRECAUTIONS

Single doses of 100 units per kg bodyweight of Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO and daily doses of 200 units per kg bodyweight of FEIBA VH IMMUNO should not be exceeded. Patients given single doses of 100 units FEIBA VH IMMUNO per kg bodyweight should be monitored for the development of DIC or symptoms of acute coronary ischemia.

High doses of FEIBA VH IMMUNO should be given only as long as absolutely necessary to stop bleeding. In case of changes in blood pressure, pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly and appropriate diagnostic and therapeutic measures are to be initiated.

Laboratory indications of DIC are decreased fibrinogen, decreased platelet count, and/or presence of fibrin-fibrinogen degradation products (FDP). Other indications of DIC include significantly prolonged thrombin time, prothrombin time, or partial thromboplastin time.

Tests used to control efficacy such as APTT, WBCT, and TEG do not correlate with clinical improvement. For this reason, attempts at normalizing these values by increasing the dose of FEIBA VH IMMUNO may not be successful and are strongly discouraged because of the potential hazard of producing DIC by overdosage.

Drug Interactions

It has been reported that FEIBA VH IMMUNO and antifibrinolytics have been given simultaneously without complications. It is, however, recommended not to use antifibrinolytics until 12 hours after the administration of FEIBA VH IMMUNO.

Pregnancy Category C

Animal reproduction studies have not been conducted with FEIBA VH IMMUNO. It is also not known whether FEIBA VH IMMUNO can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FEIBA VH IMMUNO should be given to a pregnant woman only if clearly needed.

Pediatric Use

No data are available regarding the use of FEIBA VH IMMUNO in newborns.

ADVERSE REACTIONS

After application of high doses (single infusion of beyond 100 units per kg of weight, and daily doses of 200 units per kg of body weight) of Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, laboratory and/or clinical signs of DIC have occasionally been observed.

As with all human plasma products, any kind of allergic reaction may be seen, ranging from mild, short-term urticarial rashes to severe anaphylactoid reactions.

Administration of FEIBA VH IMMUNO should be discontinued immediately, if such signs appear. Allergic Reactions should be treated with antihistamines and glucocorticoids. Shock should be treated in the usual way.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Clinical trials⁵⁻⁷ have demonstrated that the response to treatment with Anti-Inhibitor Coagulant Complex, FEIBA VH IMMUNO, may differ from patient to patient with no correlation to the patient's inhibitor titer.

Response may also vary between different types of hemorrhage (e.g. joint hemorrhage vs. CNS hemorrhage).

As a general guideline a dosage range of 50 to 100 IMMUNO Units of FEIBA VH IMMUNO per kg of body weight is recommended. However, care should be taken to distinguish between the following four indications, all of which have undergone careful clinical evaluation:

Joint Hemorrhage

In joint hemorrhage, a dose of 50 units per kg of body weight is recommended at 12-hour intervals, which may be increased to doses of 100 units per kg of body weight at 12-hour intervals.

Treatment should be continued until clear signs of clinical improvement appear, such as relief of pain, reduction of swelling or mobilization of the joint.

Mucous Membrane Bleeding

A dose of 50 units per kg body weight is recommended to be given at 6-hour intervals under careful monitoring (visible bleeding site, repeated measurements of the patient's hematocrit). If higher dosages are given, take care to prolong dosage intervals so as to make certain that a maximum daily dosage of 200 units per kg of body weight is not exceeded.

Soft Tissue Hemorrhage

For serious soft tissue bleeding, such as retroperitoneal bleeding, doses of 100 units per kg of body weight at 12-hour intervals are recommended. A daily dosage of 200 units per kg of body weight should not be exceeded.

Other Severe Hemorrhages

Severe hemorrhages, such as CNS bleedings have been effectively treated with doses of 100 units per kg of body weight at 12-hour intervals. When, in order to achieve a clear clinical improvement, the dosage intervals must be shortened, it is to be ensured that a daily dosage of 200 units per kg of body weight is not exceeded.

Reconstitution

Instructions for use for BAXJECT II Hi-Flow:

Reconstitution of powder to prepare a solution for injections

Use aseptic technique throughout entire procedure.

1. Warm the unopened vial containing the solvent (Sterile Water for Injection, EP) to room temperature, e.g. using a sterile water bath for warming within several minutes (max. +37°C).
2. Remove the protective caps from the FEIBA vial and solvent vial and cleanse the rubber stoppers with germicidal solution of both and allow to dry. Place the vials on a flat surface.
3. Open the package of BAXJECT II Hi-Flow device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the transfer device from the package.
4. Turn the package over and insert the clear plastic spike through the solvent stopper (Fig. b). Grip the package at its edge and pull the package off BAXJECT II Hi-Flow (Fig. c). Do not remove the blue cap from BAXJECT II Hi-Flow.

5. With the transfer device attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the purple plastic spike of BAXJECT II Hi-Flow through the FEIBA vial stopper. The vacuum will draw the solvent into the FEIBA vial (Fig. d).

6. Swirl gently until all the material is dissolved. Ensure that FEIBA is completely dissolved, otherwise active material will not pass through the device filter.

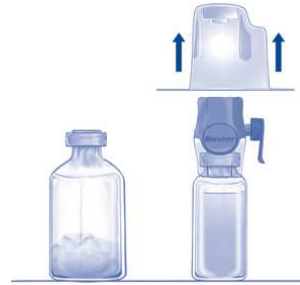
Fig. a



Fig. b



Fig. c



Injection/Infusion

Use aseptic technique throughout entire procedure.

1. Remove the blue cap from BAXJECT II Hi-Flow. Take the syringe and connect it to BAXJECT II Hi-Flow (DO NOT DRAW AIR INTO THE SYRINGE) (Fig. e).

2. Invert the system (with FEIBA vial on top). Draw the FEIBA solution into the syringe by pulling the plunger back slowly (Fig. f).

3. Disconnect the syringe.

4. Slowly inject the solution intravenously with a winged set for injection.

Fig. d



Fig. e

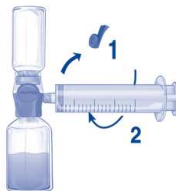
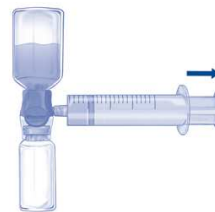


Fig. f



Do not exceed an infusion rate of 2 U FEIBA/kg Body Weight per minute.

Do not refrigerate after reconstitution!

After complete reconstitution of FEIBA VH IMMUNO its injection or infusion should be commenced as promptly as practicable, but must be completed within three hours following reconstitution.

The solution must be given by intravenous injection or intravenous drip infusion and the maximum injection or infusion rate must not exceed 2 units per kg of body weight per minute. In a patient with a body weight of 75 kg, this corresponds to an infusion rate of 2.5 - 7.5 mL per minute depending on the number of units per vial (see label on vial).

PHARMACEUTICAL INFORMATION

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, is a freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity. *In vitro*, FEIBA VH IMMUNO shortens the activated partial thromboplastin time (APTT) of plasma containing Factor VIII inhibitor. Factor VIII inhibitor bypassing activity is expressed in arbitrary units. One IMMUNO Unit of activity is defined as that amount of FEIBA VH IMMUNO which shortens the APTT of a high titer Factor VIII inhibitor reference plasma to 50% of the blank value. The product is intended for intravenous administration.

FEIBA VH IMMUNO contains Factors II, IX, and X, mainly non-activated, and Factor VII¹⁻³ mainly in the activated form. The product contains approximately equal unitages of Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors. In addition, 1 -6 units of Factor VIII coagulant antigen (F VIII C: Ag) per mL are present. The preparation contains only traces of factors of the kinin generating system. It contains no heparin.

Reconstituted FEIBA VH IMMUNO contains 4 mg of trisodium citrate x 2 H₂O and 8 mg of sodium chloride per mL.

FEIBA VH IMMUNO has been prepared from Source Plasma and/or Fresh Frozen Plasma.

The product has been subjected to in-process virus inactivation where vapor is first applied for 10 hours at 60° ± 0.5°C and an excess pressure of 190 ± 20 m bar followed by 1 hour at 80° ± 0.5°C and an excess pressure of 370 ± 30 mbar. (Refer to Clinical Pharmacology and Warnings section.)

Individual donations of human plasma are combined to form plasma pools. Prior to being used for manufacture of FEIBA VH IMMUNO, each plasma pool is tested for the presence of genome sequences of the human immunodeficiency virus type 1 (HIV-1), hepatitis B virus (HBV), and hepatitis C virus (HCV) using HIQ-PCR¹.

To prevent the transmission of infective agents by the administration of FEIBA VH IMMUNO, prescribed procedures are followed for the collection and testing of the source plasma and during the manufacture of the product. They include measures taken for donor and plasma selection, as well as virus removal and inactivation steps during manufacturing.

¹ HIQ-PCR: IMMUNO Quality-Assured Polymerase Chain Reaction with this method 500 genome equivalents/ml of the above viruses can be determined reliably, with the actual sensitivity of HIQ-PCR being below that. Therefore all pools which have been tested and evaluated as being positive lead to exclusion from further processing. No correlation has been demonstrated between infectivity and removal of pools containing these levels of genomic equivalents from further manufacturing.

Stability and Storage Recommendations

Store at refrigerator temperature (2° to 8°C, 35° to 46°F).

Avoid freezing, which may damage the diluent bottle.

Within the indicated 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.

FEIBA VH IMMUNO must not be used beyond the expiry date indicated on the label.

Reconstituted Solutions

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO is to be reconstituted only immediately before administration. The solution should then be used promptly. Any unused solution must be discarded.

AVAILABILITY OF DOSAGE FORMS

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO is supplied as freeze-dried powder, accompanied by a suitable volume of Sterile Water for Injection, E. P. and a Baxject II Hi-Flow device. The number of IMMUNO Units of Factor VIII inhibitor bypassing activity is stated on the label of each bottle.

PHARMACOLOGY

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, is an activated prothrombin complex preparation. Although Anti-Inhibitor Coagulation Complex, Vapor Heated, FEIBA VH IMMUNO, contains the coagulation factors of the prothrombin complex, it differs from the non-activated preparations in that it contains high quantities of FEIB-Activity (Factor VIII Inhibitor Bypassing Activity), which is expressed in arbitrary units, depending on the manufactured lot.

Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, has been developed for the treatment of patients with inhibitors to coagulation factors, in particular patients with inhibitors to factor VIII in whom factor VIII-preparations have a limited efficacy. Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, has been shown to correct defective coagulation in that its FEIBA-Activity bypasses the inhibitor, initiating the clotting mechanism in a stage where factor VIII is no longer required. The mechanism which produces the bypass has been investigated *in vitro* by several authors^{2,3,17-19}.

Some of the preclinical investigations were initiated and conducted only after Anti-Inhibitor Coagulant Complex, FEIBA IMMUNO, had already been administered successfully in patients with defective coagulation systems and inhibitors. The early use in humans seemed to be justified because the composition of Anti-Inhibitor Coagulant Complex, FEIBA IMMUNO, as an activated prothrombin complex preparation, differed only slightly from that of non-activated prothrombin complex preparations. Another argument in support of clinical use was the absence of an adequate animal model that would be comparable with Factor VIII inhibitor patients, and this holds true up to this very moment. When preclinical studies were conducted at a later stage, this was done primarily with the object of characterizing the activated prothrombin complex preparation, which was important also for the future development of the product. It is important to note therefore that both toxicity and thrombogenicity tests were done on animals with normal coagulation systems and do therefore not permit comparison with patient groups for whom activated prothrombin complex preparations are indicated. As with all human blood products multiple use in one and the same animal is not possible because of the antigenicity of the test material.

What has been said about safety tests also holds true for efficacy tests. There are no animal models which could be correlated with the patient groups described above. Investigations in hemophilic dogs cannot be used to evaluate efficacy, as hemophilic patients without inhibitor will not be given Anti-Inhibitor Coagulant Complex, Vapor Heated, FEIBA VH IMMUNO, either.

***In Vitro* Tests**

These tests were conducted to demonstrate that Anti-Inhibitor Coagulant Complex, FEIBA IMMUNO, has a composition similar to that of non-activated prothrombin complex preparations. The results of the tests performed on eight lots of FEIBA IMMUNO, demonstrated that FEIBA IMMUNO, contains approximately equal activities of factors II, VII, IX, and X - expressed in units of factors II, VII, IX, and X - and FEIBA-activity, expressed in IMMUNO Units. One bottle of FEIBA IMMUNO, contains between 440 and 660 IMMUNO Units, 550 and 750 Units of factor II, 411 and 809 Units of factor VII, 336 and 871 Units of factor

IX, and 480 and 560 Units of factor X. Factor VII activity is present mainly as activated factor VII: between 89 and 98% of the total factor VII activity in FEIBA IMMUNO, is activated factor VII activity.

***In Vivo* Test for Potential Thrombogenicity**

Results of the tests carried out according to Wessler on eight lots of FEIBA IMMUNO showed that 4 IMMUNO Units/kg of body weight produced no significant thrombogenic reaction; the tests using 10 Units/kg of b.w. demonstrated varying degrees of thrombogenicity; in general, 25 Units/kg of b.w. produced a thrombogenic reaction with one large thrombus in a vein segment.

These results cannot and should not be used to interpret the efficacy of Vapor Heated, FEIBA VH IMMUNO. Neither have these data unrestricted validity for safety evaluation, since this is a "venous stasis test" performed in rabbits with normal blood coagulation, and the results therefore cannot be compared to clinical results in inhibitor patients with impaired coagulation systems.

In general, clinical experience has shown FEIBA IMMUNO not to produce thrombogenic reactions in dosages of up to 100 IMMUNO Units/kg of body weight. In the Wessler Test 4 IMMUNO Units/kg of b .w. are not thrombogenic, while higher doses may have thrombogenic effects.

TOXICOLOGY

Acute Toxicity (LD₅₀)

Results of the tests performed on eight lots of FEIBA IMMUNO showed the median lethal dose to lie between 1380 and 3197 IMMUNO Units/kg of body weight; allowing for standard deviation the values ranged between 1118 and 3852 IMMUNO Units/kg of body weight. With two lots the LD₅₀ was higher than 4000 IMMUNO Units/kg of body weight and could not be calculated. The LD₅₀ in mice therefore lies between 14 and 32 times the maximum human dose (100 IMMUNO Units/kg of body weight).

The mice in general died between 24 and 72 hours after injection of the samples. Post mortem examination on the dead mice showed bleedings in the thoracic and abdominal cavities.

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