IMMUNO

AKTIENGESELLSCHAFT FÜR CHEMISCH-MEDIZINISCHE PRODUKTE

PRODUKTIONSBETRIEBE:
ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES. M. B. H. IMMUNO DIAGNOSTIKA GES. M. B. H.

IMMUNO LTD.

Att. Mr. Nicholson

Arctic House,
Rye Lane,
Dunton Green, Nr. Sevenoaks
KENT TN14 5HB
G r e a t B r i t a i n

INDUSTRIESTRASSE 72
A-1220 WIEN

TELEFON: (0222) 2300-0 (Zentrale)
GRO-C /DW ...
TELEGRAMME: IMMUNO WIEN
TELEX: 132722 imuno a
134865 imuno a

Vienna, Nov. 29, 1984
1573/Hb

Re: Amendment of PROTHROMPLEX^{R} TIM 4 and
of FEIBA Immuno^{TM} TIM 4

Dear Mr. Nicholson,

Enclosed please find the following data on the above 2 products:

1. Methods of Manufacture
2. Statements ("To whom it may concern") with Evaluation of Heat Treatment
3. Analytical Reports
4. Drafts of leaflets
5. Drafts of packaging elements

As agreed in our telephone conversation of yesterday we are sending you a standard "Method of Manufacture" for FEIBA Immuno^{TM} TIM 4 which complies, however, with the data originally submitted for our product license application except for the heat treatment step.

As we have also discussed by telephone the drafts of the labels and packaging elements for FEIBA Immuno™ TIM 4 are based on the drafts originally submitted for the FEIBA Immuno™ product license application.
The indications have been limited to haemophilia A patients with Factor VIII inhibitors and to patients with acquired Factor VIII inhibitors.

Sincerely yours,
IMMUNO AG

Enclosures

GRO-C

for Dipl.Dolm. I. Diernhofer
Licensing Department

ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE

GESELLSCHAFT M. B. H.

PRODUKTIONSBETRIEB DER IMMUNO AKTIENGESELLSCHAFT

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134925 imuno a

TO WHOM IT MAY CONCERN

We would like to draw your attention to the fact that in the manufacture of FEIBA® a Heat Treatment has been added to decrease the risk of transmitting viral diseases.

The preservation of the molecular integrity, the potency, the in vivo efficacy (in vivo recovery and biological half life) and safety of the preparation are prerequisites for the product specific Heat Treatment of coagulation factor concentrates.

The FEIBA manufactured according to the amended methodology is denominated FEIBA® TIM 4.

Methodology

As shown in the attached description of manufacture (encl. 1) the following step is performed: Heat Treatment for 10 hours at 80°C.

ÖSTERREICHISCHES INSTITUT
FÜR HAEMODERIVATE GES.M.B.H.

GRO-C

Dr. Otto F. Schwarz
Managing Director - Production

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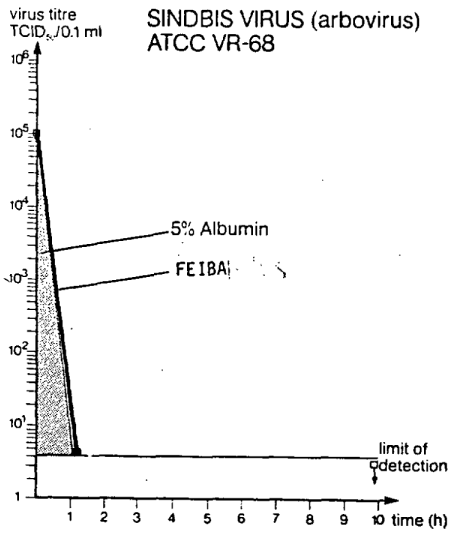
EVALUATION OF HEAT TREATMENT (TIM 4)

1) **Inactivation of Model Viruses by Heat Treatment**

Inactivation rate of model viruses obtained with Heat Treatment (TIM 4) compared with the inactivation rate in 5 % Human Albumin Solution as reference procedure*.



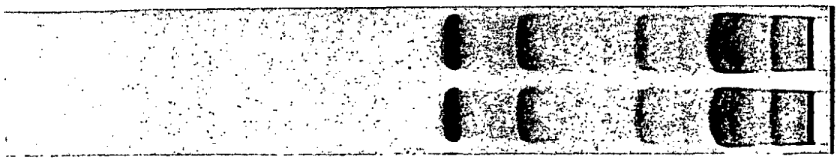
Heat Treatment (TIM 4) of FEIBA® reduces the titre of Sindbis virus by at least 4.5 log steps in 1 hour.

*) In 1947 GELLIS et al. first described the heat treatment of human albumin which today is stipulated by pharmacopoeias as mandatory and is used by all manufacturers of albumin. Since the introduction of a heat treatment step (10 h, 60°C) in the manufacture of albumin no cases of transmission of viral hepatitis or any other viral disease have been reported.

2) **Comparison of Test Results for Molecular Integrity and Acute Toxicity Carried out on Feiba® TIM 4 Before and After Heat Treatment**

- SDS-POLYACRYLAMIDE-GEL-ELECTROPHORESIS with silver staining
  The comparison of heat treated (TIM 4) and untreated material demonstrates that the protein structure remains unaltered after Heat Treatment.

Untreated FEIBA®



FEIBA® Heat Treated (Method TIM 4)

No formation of neoproteins

- ACUTE TOXICITY
  The comparison of LD_{50} results in mice (i.v.) shows that heat treatment (TIM 4) has no influence on the acute toxicity of the product.

I testify that the supplied data concerning the technical-pharmaceutical characteristics and control methods of the medicinal speciality have been checked by myself and correspond to the results of the tests performed.

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Dr. Otto F. Schwarz
Managing Director - Production

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METHOD OF MANUFACTURE

1. Product

FEIBA IMMUNO® TIM 4
Factor Eight Inhibitor Bypassing Fraction Human
250, 500 and 1000 Units*
lyophilized

2. Name and Address of Manufacturer

ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.
Industriestraße 72, A-1220 Vienna, Austria
Production Division of IMMUNO AG Vienna

3. Source Material

Single Donor Plasma (Human) and Source Plasma (Human) meeting the official requirements as outlined in the US Code of Federal Regulations 21, § 640.30 and § 640.60 respectively.

4. Method of Processing

Frozen plasma is thawed and the formed cryoprecipitate is separated by centrifugation. For generation of Factor Eight Inhibitor Bypassing Activity the cryosupernatant is adsorbed onto a slightly basic anion exchanger (DEAE-Sephadex). The protein DEAE-Sephadex complex is separated and subjected to a buffer solution treatment for separating the inert protein.

* 1 Unit is defined as the Factor Eight Inhibitor Bypassing Activity shortening the activated PTT of a high titer Factor VIII Inhibitor Reference Plasma to 50 % of the blank value.

84-11-30/UH/Z/GB

The adsorbed protein is eluted with a buffer solution. The eluate is dialyzed and the dialysate is lyophilized. The Bulk Powder I is dissolved, salts are added and the solution is subjected to a clarifying filtration. The Bulk Powder II, which is obtained after freeze drying and heat treatment, is assayed for Factor Eight Inhibitor Bypassing Activity and dissolved according to the results of the assay. The bulk solution is passed through sterile, bacteria-retaining membrane filters (pore size 0.2 µm) and then filled into R/C vials under sterile conditions. Subsequently the product is lyophilized.

5. Final Containers

R/C vials: borosilicate glass of hydrolytic class I, siliconized.

5.1. Cleaning of Final Containers and Closures

Glass Vials

The glass vials are alternately sprayed out 4 times with filtered, demineralized water and blown out with oil-free, filtered compressed air. Then they are siliconized. Subsequently the vials are continuously sterilized in a sterilization tunnel by heating to 300°C for 5 min.

Rubber Stoppers

The rubber stoppers are first rinsed twice with demineralized, filtered water at 35°C, then washed with demineralized, filtered water at 90°C and finally rinsed with demineralized, filtered water at 35°C.

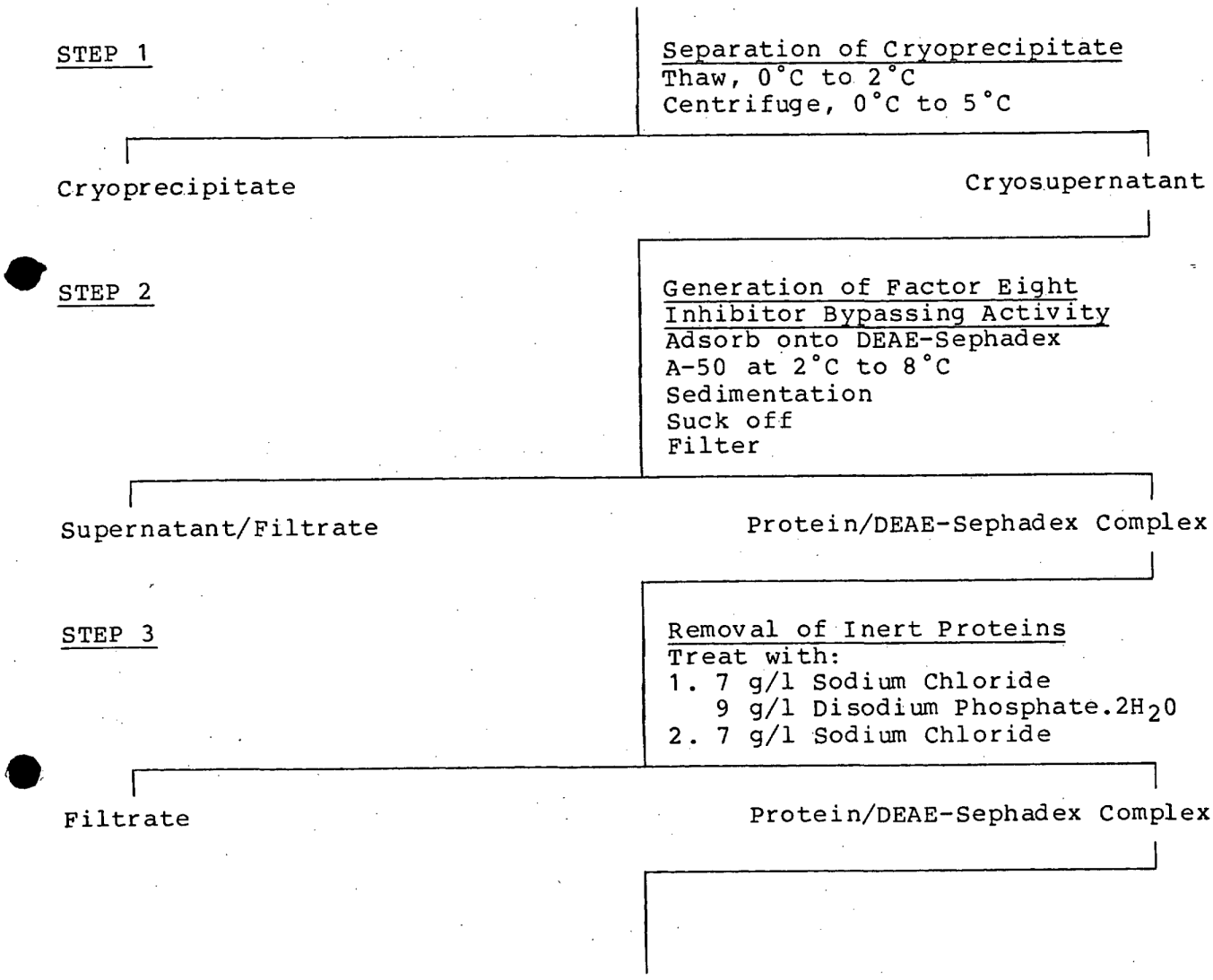
Subsequently the stoppers are siliconized and sterilized for 1 hour at 121°C in a steam autoclave.

FLOW SHEET

FOR

FEIBA IMMUNO® TIM 4

Single Donor Plasma (Human)
Source Plasma (Human)



84-11-30/UH/Z/GB

STEP 4 — Elution
30 g/l Sodium Chloride
Filter

Residue

Filtrate

STEP 5 — Dialysis
Purified water
2°C to 8°C

STEP 6 — Freeze-drying

Bulk Powder I

STEP 7 — Reconstitution of One or More Batches Bulk Powder I
a. Adjust to 50,000 Units of FEIBA®/l
b. Add 4 g/l Sodium Citrate . $2H_2O$
8 g/l Sodium Chloride
adjust the pH to 7 to 7.2 with 0.5 mol/l HCl

STEP 8 — Clarifying Filtration

STEP 9 — Freeze-drying

STEP 10 — Heat Treatment
10 hours, 80°C - 81°C

Bulk Powder II

STEP 11 — Reconstitution of Bulk Powder II
Adjust the concentration to:
12,500 Units of FEIBA®/l
25,000 Units of FEIBA®/l
50,000 Units of FEIBA®/l

STEP 12 — Sterilizing Filtration

Final Bulk

STEP 13 — Sterile Filling
250 U into 20 ml
500 U into 20 ml
1000 U into 20 ml

STEP 14 — Freeze-drying

STEP 15 — Quality Control

STEP 16 — Labeling and Packaging

Final Product
Identity Test

ÖSTERREICHISCHES INSTITUT
FÜR HAEMODERIVATE GES.M.B.H.

GRO-C

Dr. Otto F. Schwarz
Managing Director - Production

ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE

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ANALYTICAL REPORT

ON HEAT TREATMENT IN THE MANUFACTURING PROCESS OF

F E I B A ^{R} I M M U N O T I M 4

A number of tests were performed to find out whether the heat treatment during the manufacturing of FEIBA^{R} IMMUNO to decrease the risk of the transmission of viruses has any effect on the quality of the the product with respect to the following parameters:

1) potency and molecular integrity
2) innocuity
3) solubility of the product

ad 1) The determination of Factor VIII Inhibitor Bypassing Activity, tests for non-activated clotting factors (II, VII, IX and X) and determination of VIIa, Xa, Thrombin and NAPTT) showed that no significant change of the product can be observed due to the heat treatment step.

84-11-27/IH/K/M

By SDS-polyacrylamide-gel-electrophoresis and silver staining it was proved that the heat treatment does not alter the specific electropherogram of the product.

ad 2) To prove that the heat treatment has no influence on innocuity of the product, it was tested for acute toxicity and potential thrombogenicity.

For testing of acute toxicity the LD_{50} was determined. At least three different doses of the product were injected intravenously into 10 test animals per dose. After an observation period of at least 7 days the dead animals of each individual test group were counted. The cause of death was determined in each case by autopsy. By definition, the LD_{50} value is the dose which leads to the death of 50% of the test animals under the prescribed testing conditions. This value is calculated according to WILSON, E.B., WORCESTER, J.: The determination of LD_{50} and its sampling error in bio-assay, II. Proc. N.A.S. USA, Vol. 29, 1943, p. 114 - 120; WORCESTER, J., WILSON, E.B.: A table determining LD_{50} or the fifty per cent endpoint, Proc. N.A.S. USA, Vol. 29, 1943, p. 207 - 212) or according to the KÄRBER and SPAERMAN, SPAERMAN, C.: The Method of Right and Wrong Cases (Constant Stimuli) without Gauss' Formulae, Brit. Jour. of Psych., 2, 1908.
A comparison of the LD_{50} calculated as above on the heat treated and the untreated product showed that the heat treatment does not have any measurable influence on the acute toxicity of the product.

"In vivo" tests in rabbits for potential thrombogenicity proved that the heat treatment does not influence the potential thrombogenicity of the product (WESSLER, S., REIMER, S.M. + SHEPS, M.C.: Biologic assay of a thrombosis-inducing activity in human serum. J. Appl. Physiol 14: 943 - 946, 1959)

ad 3) Solubility tests showed that the heat treatment does not have any measurable influence on the solubility of the product if reconstituted as prescribed by the manufacturer.

The results of the above tests prove that the change in the manufacturing process does not have any measurable influence on the quality of the product.

ÖSTERREICHISCHES INSTITUT
FÜR HAEMODERIVATE GES.M.B.H.

GRO-C

Dr. Herwig Igel
Head, Quality Control -
Blood Derivatives

GENEHMIGUNG DES LÄNDERSPEZIFISCHEN* LABELING

- o BEIPACKTEXT
- o ETIKETTIERUNG

für Produkt FEIBA IMMUNO TM TIM 4

Land ENGLAND

Nr. _____ Datum _____

Ländersachbearbeiter Registrierungsabt _____ am _____

Abteilungsleiter Registrierungsabt. _____ am _____

Übersetzer _____ am _____

Product Manager
oder Leiter Marketing ** GRO-C: Koil am 29.11.84

Klinische Forschung ** _____ am _____

AL der Abteilung IND (nur bei USA) _____ am _____

zuständiger Konzessionär _____ am _____

* gilt für alle Beipacktexte in deutsch, englisch, französisch italienisch, spanisch

** bei sachlichen Änderungen, bei USA in jedem Fall

Please note that wherever the name "FEIBA IMMUNO" appears in the leaflet this will be replaced by the name "FEIBA IMMUNO TIM 4" in the final version.

FEIBA IMMUNO ™ TIM 4

Factor VIII Inhibitor Bypassing Fraction Human

heat-treated

CHARACTERISTICS AND COMPOSITION

FEIBA IMMUNO is a human plasma fraction with Factor VIII inhibitor bypassing activity shortening the activated PTT of plasma containing a Factor VIII inhibitor. The FEIB-activity is measured by determining the shortening of the activated PTT of a standard Factor VIII inhibitor plasma, and is expressed in FEIBA-units*.

To decrease the potential risk of transmission of viral hepatitis and other viral infections the following steps are taken:

1. Donor and Plasma Selection:
   All donations and pools of plasma used in the manufacture of FEIBA IMMUNO TIM 4 and the final product were tested for HBs-antigen by Radio Immune Assay (RIA) and found non-reactive.
2. Thermoinactivation by Method TIM 4:
   FEIBA IMMUNO TIM 4 is subjected to a model virus controlled product specific thermoinactivation.

Tests on FEIBA IMMUNO TIM 4 also include absence of pyrogens, sterility, and innocuity.

INDICATIONS

Feiba's most important indication is the control of bleeding episodes in haemophilia A patients with Factor VIII inhibitors and in patients with acquired Factor VIII inhibitors.

cf. Tel. c. Mrs. Nicholson

GRO-C

Feiba is indicated for the control of ....

ADMINISTRATION

FEIBA IMMUNO must be dissolved immediately before injection using the amount of solvent provided.

Directions for Reconstitution of a Solution for Injection

1. Warm solvent to room temperature.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Transfer of the solvent into the bottle containing the lyophilisate is done with the help of the transfer needle. For this purpose first remove the protective cap of the transfer needle and insert it into the rubber stopper of the bottle containing the solvent (fig. 2). Then remove the protective tube of the transfer needle. Turn the solvent bottle with the inserted transfer needle upside-down and insert the latter into the rubber stopper of the lyophilisate bottle leaving a free needle length of 1 cm outside the bottle (fig. 3). Caution: do not touch the needle!
   Because of the vacuum in the lyophilisate bottle the solvent will then run in.
4. Remove the solvent bottle with the transfer needle from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.
5. Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.
6. Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).
7. Separate the syringe from the filter needle and fit the enclosed disposable needle (or winged adapter needle). Slowly inject the solution intravenously at a maximum rate of 2 U/kg/min.

* 1 FEIBA unit is defined as the FEIB-activity shortening the activated PTT of a high titre Factor VIII Inhibitor Reference Plasma (IMMUNO House Standard) to 50 per cent of the blank value.

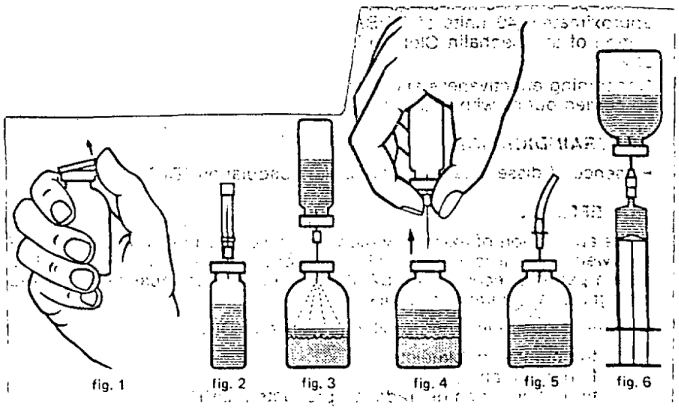

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

Do not exceed the maximum injection rate of 2 U/kg/min.

The solution must be injected through a filter if a different method of reconstitution is used.

DOSAGE AND FREQUENCY OF APPLICATION

Factor VIII-Inhibitor Patients

On the basis of available clinical trial results obtained in the treatment of Factor VIII inhibitor patients it is possible that FEIBA's effectiveness may vary between patients; this may be due to varying inhibitor titres and other, as yet unknown, factors. As a result larger doses may be necessary if the inhibitor titres are high, but this is not a general rule.

The determination of the Whole Blood Clotting Time (WBCT) according to Lee White and/or the calculation of the r-value in the thrombelastogram (TEG) help to determine the most effective dose and to check the success of therapy.

Care must be taken to distinguish between the following indications:

Spontaneous bleeding episodes

A dosage of 50 to 100 units per kg bodyweight, administered in 8- to 12-hourly intervals is recommended and should be continued until clear signs of therapeutic improvement appear. This means, in the case of exterior bleeding, healing of the bleeding site, or in the case of internal bleeding, a lessening of pain, reduction in swelling or mobilisation of the joint. If there are no signs of therapeutic improvement despite the administration of 100 units of FEIBA per kg bodyweight given 8-hourly, a combined therapy with 40 units per kg bodyweight of a Factor VIII concentrate (KRYOBULIN or FACTOR VIII CONCENTRATE HUMAN IMMUNO) is recommended. The Factor VIII must be administered after each individual dose of FEIBA.

In home treatment of bleeding complications up to 150 U/kg bodyweight have been administered, the effective dose very likely depending on the extent of bleeding. In some cases a kind of maintenance prophylaxis was successfully undertaken in home treatment with three applications weekly of approximately 30 units of FEIBA IMMUNO per kg bodyweight, followed by approximately 60 units of Factor VIII concentrate per kg bodyweight.

Minor surgery

Basically, the same kind of therapy should be followed as in the case of spontaneous bleeding episodes. It is, however, necessary to check the substitution effect before the operation and, if necessary, increase the dose or give consideration to combined treatment with Factor VIII Concentrate (40 units per kg bodyweight).

For checking effectiveness, the following tests should be carried out:

- Whole Blood Clotting Time (WBCT) according to Lee White
- r-value of the thrombelastogram (TEG).

When a combination therapy with Factor VIII concentrate is used the Activated Partial Thromboplastin Time (APTT) may be shortened to normal values.

Since disseminated intravascular coagulation (DIC) cannot be totally excluded in the course of this treatment, it is advisable to carry out repeated tests on

- platelets
- fibrinogen and
- FDP**

** Fibrin-Fibrinogen Degradation Products

CAUTION

Before each individual application of FEIBA IMMUNO with Factor VIII inhibitor patients it is advisable to count the patient's platelets, since some investigators (VERMYLEN, WENSLEY) have found that FEIBA's effectiveness depends on the presence of a normal number of platelets. If the number of platelets is below 100,000/mm³ this should be normalized by giving platelet-concentrate before administering FEIBA IMMUNO. In this connection special attention must be drawn to the platelet drop which follows the use of animal AHG, which may render FEIBA IMMUNO ineffective.

CONTRAINDICATIONS

Presence of disseminated intravascular coagulation (DIC).

SIDE EFFECTS

In the application of extremely high doses, i.e. 200 units of FEIBA per kg bodyweight or more, occasionally signs of DIC have been seen. For this reason patients receiving FEIBA IMMUNO must continually be checked for signs of accelerated coagulation.

In order to determine the possible presence of DIC

the number of platelets
fibrinogen and
fibrin-fibrinogen degradation products (FDP)

should be checked repeatedly.

Caution is necessary if

the Activated Partial Thromboplastin Time (APTT) or
Prothrombin Time

are prolonged after administration of FEIBA IMMUNO™.

If this is the case, it is absolutely necessary to carry out the three obligatory tests mentioned above. If the results point to DIC (platelet drop, fibrinogen decrease, rise in FDP) the application of FEIBA must be interrupted.

With the application of human plasma derivatives any kind of allergic reaction may be observed, ranging from mild, short-term urticarial rashes to anaphylactic shock. In these cases the application of FEIBA IMMUNO must be discontinued immediately. Allergic reactions should be treated with antihistamines ~~and gluco-corticoids~~. Shock should be treated in the usual way.

gestrichen U. Telex

GRO-C

Anamnestic reactions showing raised inhibitor titres may not be totally excluded after the application of FEIBA IMMUNO. However, some of the patients treated with FEIBA IMMUNO show lowered inhibitor titres, while the titres of the majority remain unchanged.

Despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out.

SHELF LIFE AND STORAGE

Two ... years at a temperature between +2° and +8°C.

PACKS

FEIBA IMMUNO

500 FEIBA-units
dried substance + 20 ml of **Water for Injections B.P.**

1000 FEIBA-units
dried substance + 20 ml of **Water for Injections B.P.**

All packages contain equipment for reconstitution and injection.

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Tel.: Sevenoaks (0732) 458101

Manufactured by
ÖSTERREICHISCHES INSTITUT
FÜR HAEMODERIVATE GES.M.B.H.
Production Division of
IMMUNO AG Vienna Austria

Inner Label

F E I B A I M M U N O ™ TIM 4 500

Factor VIII Inhibitor Bypassing Fraction Human
heat-treated
500 FEIBA units*

Lyophilised Prod. Lic. No.
Prepared from a plasma pool of selected HB_s-Ag negative donors

To be reconstituted with 20 ml of Water for Injections B.P.

The solution must be injected intravenously immediately after reconstitution.

* One FEIBA unit is defined as the FEIB-activity shortening the activated PTT of a high titre Factor VIII Inhibitor Reference Plasma (Immuno House Standard) to 50 per cent of the blank value

For reconstitution observe the directions given in the circular enclosed.

1 ml of the reconstituted solution contains:

FEIBA	25 units*
Total protein	10-30 mg
Trisodium citrate .$2H_2O$	4 mg
Sodium chloride	8 mg

Contains no preservative

Store between +2° and +8°C

P.O.M.

Batch No.:

Exp. Date:

Distributed by IMMUNO LTD
Arctic House, Rye Lane, Dunton Green,
Nr. Sevenoaks, Kent TN14 5HB
Tel.: Sevenoaks (0732) 458101
Manufactured by ÖSTERREICHISCHES
INSTITUT FÜR HAEMODERIVATE GES.M.B.H.
Production Division of
IMMUNO AG Vienna Austria

Label for Box

FEIBA IMMUNO ™ TIM 4 500

500 FEIBA units*

FEIBA IMMUNO ™ TIM 4 500

Factor VIII Inhibitor Bypassing Fraction Human
heat-treated
500 FEIBA units*

Prod. Lic. No.

Batch No.:

Exp. Date:

P.O.M.

Store between +2° and +8°C

Nr. Sevenoaks, Kent TN14 5HB
Tel.: Sevenoaks (0732)458101

FEIBA IMMUNO ™ TIM 4 500

Factor VIII Inhibitor Bypassing Fraction Human
heat-treated
500 FEIBA units*

Lyophilised
Prepared from a plasma pool of selected HB_s-Ag negative donors

To be reconstituted with 20 ml of Water for Injections B.P.

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Production Division of IMMUNO AG Vienna Austria

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Factor VIII Inhibitor Bypassing
Fraction Human
heat-treated

500 FEIBA units*

FEIBA IMMUNO ™ TIM 4 500

Factor VIII Inhibitor Bypassing
Fraction Human
heat-treated
500 Feiba units*

Lyophilised Product Licence No.

Prepared from a plasma pool of selected HB_S-Ag negative donors

To be reconstituted with 20 ml of Water for Injections B.P.

For reconstitution observe the directions given in the circular enclosed

Enclosed: 20 ml of Water for Injections B.P.
Kit for reconstitution and injection

The solution must be injected intravenously immediately after reconstitution

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Contains no preservative

P.O.M.

Store between +2° and +8°C

If cold storage space is insufficient refrigerate only the lyophilised substance. Solvent and kit may also be stored at room temperature.

Distributed by IMMUNO LTD, Arctic House, Rye Lane, Dunton Green,Nr. Sevenoaks, Kent TN14 5HB; Telephone: Sevenoaks (0732) 458101
Manufactured by ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.
Production Division of IMMUNO AG Vienna Austria

FEIBA IMMUNO ™ TIM 4 500

Factor VIII Inhibitor Bypassing
Fraction Human
heat-treated

500 FEIBA units*

Outer Label

Inner Label

F E I B A I M M U N O ™ TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human
heat-treated
1000 FEIBA units*

Lyophilised Prod. Lic. No.
Prepared from a plasma pool of selected HB_s-Ag negative donors

To be reconstituted with 20 ml of Water for Injections B.P.

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For reconstitution observe the directions given in the circular enclosed.

1 ml of the reconstituted solution contains:

FEIBA	50 units*
Total protein	20-60 mg
Trisodium citrate $\cdot 2H_2O$	4 mg
Sodium chloride	8 mg

Contains no preservative

Store between +2° and +8°C

P.O.M.

Batch No.:

Exp. Date:

Distributed by IMMUNO LTD
Arctic House, Rye Lane, Dunton Green,
Nr. Sevenoaks, Kent TN14 5HB
Tel.: Sevenoaks (0732) 458101

Manufactured by ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.
Production Division of
IMMUNO AG Vienna Austria

Label for Box

FEIBA IMMUNO TM TIM 4 1000

1000 FEIBA units*

FEIBA IMMUNO TM TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human heat-treated

1000 FEIBA units*

Prod. Lic. No.

Batch No.:

Exp. Date:

P.O.M.

Store between +2° and +8°C

Nr. Sevenoaks, Kent TN14 5HB
Tel.: Sevenoaks (0732)458101

FEIBA IMMUNO TM TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human heat-treated

1000 FEIBA units*

Lyophilised
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Manufactured by ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.

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Production Division of IMMUNO AG Vienna Austria

FEIBA IMMUNO TM TIM 4 1000

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Arctic House, Rye Lane,
Dunton Green,

FEIBA IMMUNO TM TIM 4 1000

1000 FEIBA units*

Outer Label

FEIBA IMMUNO TM TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human heat-treated

1000 FEIBA units*

Lyophilised Product Licence No.

Prepared from a plasma pool of selected HB_s-Ag negative donors

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FEIBA IMMUNO TM TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human heat-treated

1000 FEIBA units*

1 ml of the reconstituted solution contains:

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Trisodium citrate • $2H_2O$	4 mg
Sodium chloride	8 mg

Contains no preservative

P.O.M.

Store between $+2^{o}$ and $+8^{o}C$

If cold storage space is insufficient refrigerate only the lyophilised substance.
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FEIBA IMMUNO TM TIM 4 1000

Factor VIII Inhibitor Bypassing Fraction Human heat-treated

1000 FEIBA units*

Unterlagen v. Dr. Koch Nov. 84

83-12-06/MK/sch

ORIGINAL PACKAGE INSERT ENGLISH
TIM X+) PRODUCTS

3

To decrease the potential risk of transmission of viral hepatitis and other viral infections the following steps are taken:

1. Donor and Plasma Selection:

[Hepatitis B:] All donations and pools of plasma used in the manufacture of ..... and the final product were tested for HBs-antigen by Radio Immune Assay (RIA) and found non-reactive.

[Non-A/Non-B Hepatitis: For the manufacture of ..... only single donor plasma of ALT-levels* of ≤ 25 U/l** is used.]

Bei ROT hinein, bei BLAU heraus

2. Thermoinactivation by "Method X":

..... is subjected to a model virus controlled product specific thermoinactivation. [(TIM. Thermoinactivation Method IMMUNO).]

4. 11. 84.

Under Adverse Reactions:

taken to reduce the risk,

3. Despite these measures the transmission of viral hepatitis or other viral infections cannot be ~~eliminated entirely.~~ ruled out.

+) Coagulation Factor Concentrates TIM 2, 3, 4, etc.

* Increased ALT-levels in the plasma of donors are associated with an increased risk of transmission of non-A/non-B hepatitis (AACH et al., 1981, ALTER et al., 1981).

** Optimized test at 25°C: Recommendations of the German Society for Clinical Chemistry; Z. Klin. Chem. Biochem. 8:658 (1970); 9:464 (1971); 10:182 (1972).

[ ] only TK-countries

GRO-C

c/F.Ma GRO-C 84-07-04