FEIBA® TIM 4 IMMUNO

Anti-Inhibitor-Coagulant Complex
Steam Treated

COMPOSITION AND PROPERTIES

FEIBA TIM 4 contains an anti-inhibitor-coagulant complex with standardised FEIB-activity[1] (Factor Eight Inhibitor Bypassing Activity);

1 mg of protein contains 0.7 to 2.5 units FEIBA.

FEIBA TIM 4 also 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 U/1 U FEIBA. The preparation contains only traces of factors of the kallikrein-kinin system, if any at all.

FEIBA TIM 4 is prepared from pooled human plasma.

All plasma units are exclusively obtained from licensed plasmapheresis centers in Central Europe and the United States of America.

For the manufacture of FEIBA TIM 4 only plasma units are used which were ALT-tested and were non-reactive in tests for HB_s-antigen and HIV-antibodies.

To further reduce the potential risk of viral transmission the product is steam treated under product-specific conditions (at 60°C for 10 hours, at 80°C for 1 hour) during production.

In HIV spiked samples of FEIBA TIM 4 this treatment inactivated at least 10^6 IVIU/ml^2 in 3 hours.

INDICATIONS

FEIBA TIM 4 is indicated for therapy and prophylaxis of haemorrhage and to cover surgical interventions in:

- Haemophilia A patients with F VIII inhibitor
- Haemophilia B patients with F IX inhibitor.

FEIBA TIM 4 was also used in combination with Factor VIII concentrate for a continual long term therapy to achieve a complete and permanent elimination of the F VIII inhibitor so as to allow for regular treatment with F VIII concentrate as in patients without inhibitor (BRACKMANN et al., 1981).

In addition, the successful use of FEIBA TIM 4 was described in a few non-haemophiliacs with acquired inhibitors to factors VIII,XI, and XII as well as in a patient with von Willebrand's disease with an inhibitor. For guidelines for treatment of patients with inhibitors see table 1.

Since a single dose of FEIBA TIM 4 contains considerably less F VIII coagulant antigen than Factor VIII concentrate, FEIBA TIM 4 is the treatment of choice in high responder patients, even if the current inhibitor titre is low.

CONTRAINDICATIONS

Depending on therapeutic alternatives below contraindications are to be considered relative or absolute.

In the following situations FEIBA TIM 4 should only be used if — for example owing to a very high inhibitor titre — no response to treatment with the appropriate coagulation factor concentrate can be expected.

Disseminated Intravascular Coagulation (DIC):

- Laboratory and/or clinical symptoms which are clearly indicative of DIC.
- Laboratory, histological and/or clinical signs 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:

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 TIM 4 is only indicated in life-threatening bleeding events.

SIDE EFFECTS

In rare cases allergic reactions such as fever, urticarial rashes, nausea and retching as well as other more or less severe anaphylactoid reactions have been observed after administration of FEIBA TIM 4.

Severe allergic and anaphylactoid reactions may necessitate the interruption of substitution treatment. Mild reactions can be managed with antihistamines; severe reactions require immediate intervention. In patients with a history of hypersensitivity reactions to plasma derivatives the prophylactic administration of antihistamines may be indicated.

After administration of high doses (single doses of more than 100 units FEIBA per kg of bodyweight, and daily doses of more than 200 units per kg bw.) laboratory signs such as the presence of fibrinopeptide A, fibrin/fibrinogen degradation products, or prolonged activated partial thromboplastin time (APTT), thrombin time and prothrombin time indicative of DIC (see PRECAUTIONS) were observed in a few cases. However, a severe clinical course or fatal outcome after treatment with FEIBA TIM 4 have never been reported.

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.

Clinical safety studies have shown no case of hepatitis B or NANB.

The product is safe with respect to transmission of HIV (HTLV-III/LAV).

INTERACTIONS

It is recommended not to use antifibrinolytics such as epsilon-aminocaproic acid in combination with FEIBA TIM 4 treatment (see PRECAUTIONS).

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

[2] in vitro infectious units per ml

DOSAGE AND ADMINISTRATION

As a general guideline a dose of 50 to 100 units of FEIBA per kg bodyweight is recommended, however, not exceeding a daily dose of 200 U/kg bw.

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 thrombelastogramme (TEG, r-value), and the APTT usually show only a minor shortening and need not correlate with clinical improvement. For this reason these tests can only be used for monitoring of FEIBA TIM 4 therapy to a very limited extent.

1. Spontaneous Bleeding

Joint, Muscle and Soft Tissue Haemorrhage

For minor to moderate bleedings a dose of 50 — 75 U/kg bw. 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 bw. at 12-hour intervals are recommended.

Mucous Membrane Bleeding

A dose of 50 U/kg bw. is recommended to be given at 6-hour intervals under careful monitoring of the patient (visible bleeding site, repeated measurements of the patient's haematocrit). Again, if haemorrhage does not stop, the dose may be increased to 100 U/kg bw. taking care not to exceed the maximum daily dose of 200 U/kg bw.

Other Severe Haemorrhages

Severe haemorrhages, such as CNS bleedings have been effectively treated with doses of 100 U/kg bw. at 12-hour intervals. In individual cases FEIBA TIM 4 may be given at intervals of 6 hours until clear clinical improvement is achieved. (Do not exceed the maximum daily dose!)

2. Surgery

Taking care not to exceed the maximum daily dose, 50 — 100 U/kg bw. should be given at intervals of up to 6 hours.

3. Prophylactic Treatment

For dosage recommendations for prophylactic treatment see table 2.

Reconstitution of Concentrate

FEIBA TIM 4 is to be stored in lyophilised condition and should only be reconstituted immediately before application. The solution must then be used as promptly as practicable, however, within a maximum of 1 hour. Entered vials must not be reused.

1. Warm the unopened bottle containing the solvent to room temperature (max. 37°C).
2. Remove the caps from the concentrate and solvent bottles (fig. A) and disinfect the rubber stoppers of both bottles.
3. The enclosed transfer needle (double-ended needle) is protected by 2 plastic caps sealed by a weld mark. Break the weld (fig. B) by twisting and remove one cap. Insert the exposed needle into the rubber stopper of the solvent bottle (fig. C).
4. Remove the other cap from the double-ended needle taking care not to touch the exposed end.
5. Invert the solvent bottle over the concentrate bottle, and insert the free end of the double-ended needle to approximately half the needle length into the rubber stopper of the concentrate bottle (fig. D). The solvent will be drawn into the concentrate bottle which is under vacuum.
6. Disconnect the two bottles by removing the needle from the concentrate bottle (fig. E). Gently agitate or rotate the concentrate bottle to accelerate dissolution.
7. Upon complete reconstitution of the concentrate insert the enclosed aeration needle (fig. F) and any foam will collapse. Remove the aeration needle.

Administration

Remove the protective covering from the enclosed filter needle by turning the cap and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. G).

Disconnect the filter needle from the syringe and slowly inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

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

If a different ~~reconstitution~~ method is chosen, use an appropriate filter ~~to prevent administration of undissolved particles (if rapid reconstitution is required for emergencies), of rubber particles out from the stopper, danger of microembolism~~.

PRECAUTIONS

Disseminated Intravascular Coagulation (DIC)

If clinical signs of intravascular coagulation occur, which include changes in blood pressure, pulse

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rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly and the patient monitored for DIC by appropriate laboratory tests. 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 APTT.

Laboratory Tests and Clinical Efficacy

Ex vivo tests to control efficacy such as APTT, whole blood clotting time (WBCT), and thrombelastogramme (TEG) need not correlate with clinical improvement. For this reason, attempts at normalising these values by increasing the dose of FEIBA TIM 4 may not be successful and are strongly discouraged because of the potential hazard of producing DIC by overdosage.

Significance of Platelet Count

In case of inadequate or lacking response to FEIBA TIM 4 treatment it is recommended that a platelet count be performed, since a sufficient number of functionally intact thrombocytes is considered to be necessary for the efficacy of FEIBA TIM 4.

Antifibrinolytics

If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA TIM 4 is to be carried out, the interval between the administration of either product should be at least 6 hours.

SHELF LIFE AND STORAGE

Two years when stored between +2°C and +8°C.

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 25°C). Without cooling facilities FEIBA TIM 4 may therefore be taken along when travelling or during holidays. The dates between which the product is not stored at refrigerator temperature should be noted on the package.

FEIBA TIM 4 must not be used beyond the expiry date indicated.

Store out of the reach of children.

PACKS

FEIBA TIM 4 IMMUNO 250
- R/C vial containing 250 FEIBA-units, lyophilised
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Table 1: Guidelines for Treatment of Patients with Inhibitors

Inhibitor titre (BU*/ml)	Response to F VIII treatment	Minor to moderate bleeding	Severe to life-threatening bleeding, surgery
< 5	low responder high responder	F VIII or FEIBA TIM 4 FEIBA TIM 4	F VIII or FEIBA TIM 4 FEIBA TIM 4
5 – 10	low responder high responder	F VIII or FEIBA TIM 4 FEIBA TIM 4	FEIBA TIM 4 FEIBA TIM 4
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* 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.

Table 2: Prophylactic Treatment

	Factor VIII	FEIBA	Dosage interval	Duration of treatment
Stage I	75 – 100 U/kg	40 – 60 U/kg	twice a day	until reduction of F VIII inhibitor titre to approx. 1 BU*/ml (= 0.5 Old Oxford Units/ml**)
Stage II	75 – 100 U/kg	———	twice a day	until no inhibitor is detectable
Stage III	75 – 100 U/kg	———	once or twice a day	until normal F VIII half life and in vivo recovery are obtained

* KASPER C., EWING N. P.: Experience with the bethesda assay and other methods of inhibitor detection, in MARIANI G., RUSSO M. A., MANDELLI F. (eds.): Activated Prothrombin Complex Concentrates, Praeger, New York 1982, pp. 17 – 30.

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Issued
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6205820EU06/40-8

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SIDE EFFECTS

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Severe allergic and anaphylactoid reactions may necessitate the interruption of substitution treatment. Mild reactions can be managed with antihistamines; severe reactions require immediate intervention. In patients with a history of hypersensitivity reactions to plasma derivatives the prophylactic administration of antihistamines may be indicated.

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INTERACTIONS

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DOSAGE AND ADMINISTRATION

As a general guideline a dose of 50 to 100 units of FEIBA per kg bodyweight is recommended, however, not exceeding a daily dose of 200 U/kg bw.

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

Mucous Membrane Bleeding

A dose of 50 U/kg bw. is recommended to be given at 6-hour intervals under careful monitoring of the patient (visible bleeding site, repeated measurements of the patient's haematocrit). Again, if haemorrhage does not stop, the dose may be increased to 100 U/kg bw. taking care not to exceed the maximum daily dose of 200 U/kg bw.

Other Severe Haemorrhages

Severe haemorrhages, such as CNS bleedings have been effectively treated with doses of 100 U/kg bw. at 12-hour intervals. In individual cases FEIBA TIM 4 may be given at intervals of 6 hours until clear clinical improvement is achieved. (Do not exceed the maximum daily dose!)

2. Surgery

Taking care not to exceed the maximum daily dose, 50 — 100 U/kg bw. should be given at intervals of up to 6 hours.

3. Prophylactic Treatment

For dosage recommendations for prophylactic treatment see table 2.

Reconstitution of Concentrate

FEIBA TIM 4 is to be stored in lyophilised condition and should only be reconstituted immediately before application. The solution must then be used as promptly as practicable, however, within a maximum of 1 hour. Entered vials must not be reused.

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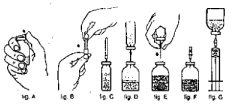
4. Remove the other cap from the double-ended needle taking care not to touch the exposed end.
5. Invert the solvent bottle over the concentrate bottle, and insert the free end of the double-ended needle to approximately half the needle length into the rubber stopper of the concentrate bottle (fig. D). The solvent will be drawn into the concentrate bottle which is under vacuum.
6. Disconnect the two bottles by removing the needle from the concentrate bottle (fig. E). Gently agitate or rotate the concentrate bottle to accelerate dissolution.
7. Upon complete reconstitution of the concentrate insert the enclosed aeration needle (fig. F) and any foam will collapse. Remove the aeration needle.



Administration

Remove the protective covering from the enclosed filter needle by turning the cap and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. G).

Disconnect the filter needle from the syringe and slowly inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

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

If a different reconstitution method is chosen, use an appropriate filter to prevent administration of undissolved particles (if rapid reconstitution is required for emergencies) or rubber particles cut from the stopper (danger of microembolism).

PRECAUTIONS

Disseminated Intravascular Coagulation (DIC)

If clinical signs of intravascular coagulation occur, which include changes in blood pressure, pulse

rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly and the patient monitored for DIC by appropriate laboratory tests. 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 APTT.

Laboratory Tests and Clinical Efficacy

Ex vivo tests to control efficacy such as APTT, whole blood clotting time (WBCT), and thrombelastogramme (TEG) need not correlate with clinical improvement. For this reason, attempts at normalising these values by increasing the dose of FEIBA TIM 4 may not be successful and are strongly discouraged because of the potential hazard of producing DIC by overdosage.

Significance of Platelet Count

In case of inadequate or lacking response to FEIBA TIM 4 treatment it is recommended that a platelet count be performed, since a sufficient number of functionally intact thrombocytes is considered to be necessary for the efficacy of FEIBA TIM 4.

Antifibrinolytics

If treatment with both antifibrinolytics such as epsilon-aminocaproic acid and FEIBA TIM 4 is to be carried out, the interval between the administration of either product should be at least 6 hours.

SHELF LIFE AND STORAGE

Two years when stored between +2°C and +8°C.

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 25°C). Without cooling facilities FEIBA TIM 4 may therefore be taken along when travelling or during holidays. The dates between which the product is not stored at refrigerator temperature should be noted on the package.

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Table 2: Prophylactic Treatment

	Factor VIII	FEIBA	Dosage interval	Duration of treatment
Stage I	75 – 100 U/kg	40 – 60 U/kg	twice a day	until reduction of F VIII inhibitor titre to approx. 1 BU*/ml (= 0.5 Old Oxford Units/ml**)
Stage II	75 – 100 U/kg	———	twice a day	until no inhibitor is detectable
Stage III	75 – 100 U/kg	———	once or twice a day	until normal F VIII half life and in vivo recovery are obtained

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6205B20EU06/40-8