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IMMUNO LTD.
Att. Mr. Coombes

Arctic House
Rye Lane
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Nr. Sevenoaks
KENT TN14 5HB
G R E A T B R I T A I N

Vienna, 89 12 20
4138/Hi/MB

Dear Mr. Coombes,

attached please find a list and copies of all UK specific KRYOBULIN and PROTHROMPLEX texts as well as of the relevant neutral English texts starting from 1980.

As already mentioned we would need further details on the lot number, date of supply, etc. in order to be able to definitely trace a text used at a specific period of time, if necessary.

Kind regards
IMMUNO AG

GRO-C

Dipl.Dolm. I. Diernhofer
Licencing Department

Encl.

SHPL0000185_0001

UK Specific Texts

PROTHROMPLEX

PROTHROMPLEX, untreated

110979

6205911EA01			VA 16.01.1986
6205911EA02	FG	20.07.1984	VA 10.07.1986

PROTHROMPLEX TIM 4, Heat Treated

6205911EA04	MWG	29.11.1984	
	FG	18.12.1984	
6205911EA06	MWG	14.12.1984	VA 10.07.1986
	FG	21.01.1985	

PROTHROMPLEX, Steam Treated (Method S-2)

6205911EA10	MWG	26.09.1985	
	FG	25.11.1986	

Neutral English Texts

PROTHROMPLEX

PROTHROMPLEX, untreated

040678

6205212EW01	FG 25.05.1983	VA 14.07.1986

PROTHROMPLEX TIM 2, Steam Treated

6205212EW51	MWG 7.02.1986 FG 27.03.1986	VA 2.07.1987

PROTHROMPLEX TIM 4, Steam Treated

6205212EW02	MWG 6.02.1986 FG 7.04.1986	VA 1.08.1989
6205212EW03	MWG 27.01.1987 FG 10.06.1987	currently used

BEBULIN TIM 2, Steam Treated (delivered in 1985)

6205911EU01	MWG 12.07.1985 FG 10.10.1985

BEBULIN TIM 4, Steam Treated (delivered in 1985)

6205911EU51	MWG 12.07.1985 FG 10.10.1985

FG - date of release of text

MWG - date of passing on of manuscript for printing

VA - date of withdrawal of text

UK SPECIFIC TEXTS

PROTHROMPLEX

[redacted]

6205911EA10

X

P.O.M

Prothromplex®
Partial Prothrombin Complex Human, Steam Treated (Method S-2)

PROTHROMPLEX contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit* of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.

To eliminate the potential risk of thrombogenic complications associated with Factor IX preparations PROTHROMPLEX is routinely tested for the absence of activated coagulation factors.

In addition, PROTHROMPLEX contains a small amount of heparin (max. 0.15 i.u. heparin per unit of Factor IX).

When using PROTHROMPLEX in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboembolism is to be expected.

PROTHROMPLEX is prepared from pooled plasma of suitable** human donors.

For the manufacture of PROTHROMPLEX only plasma donations are used which are non-reactive in tests for HB_s-antigen and HTLV-III antibodies.

Both the plasma pool and the final product are tested for the absence of HB_s-antigen; the plasma pool is also tested for the absence of HTLV-III antibodies.

The product has been treated at 60°C for 10 hours at a defined steam pressure (Method S-2).

Samples of PROTHROMPLEX, which were spiked with 2×10^6/ml infectious units of HTLV-III, did not contain viral elements capable of reproducing after the product specific steam treatment. The HTLV-III titer was determined after incubation with HT-H9 cells and subsequent measurement of reverse transcriptase activity in the clarified cell supernatant.

INDICATIONS

Treatment of cases of haemophilia B (Factor IX deficiency).
By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).

The most reliable results are obtained by quantitative activity assays of Factor IX.

RECONSTITUTION AND ADMINISTRATION

Reconstitution

PROTHROMPLEX is to be stored in the lyophilised state and should only be reconstituted immediately before application. The solution must then be used promptly. Entered vials must not be reused.

* 1 unit of Factor II, IX and X is equivalent to the Factor II, IX and X activity of 1 ml average fresh normal plasma. The Factor IX units are expressed in terms of the WHO Standard.

** Suitable human donors as described in the British Pharmacopoeia 1980 under Albumin and in compliance with the "Recommendations to Decrease the Risk of Transmitting Acquired Immune Deficiency Syndrome (AIDS) from Plasma Donors" issued by the US Food & Drug Administration, March 24, 1984.

shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.

2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.
3. The risk of transmission of viral hepatitis is most probably eliminated by careful donor and plasma selection together with steam treatment of the product.

   Transmission of HTLV-III can be effectively excluded by the above measures.

CONTRA-INDICATIONS

In patients with consumption coagulopathy administration of PROTHROMPLEX is recommended only after elimination of the underlying consumption disorder.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6°C, protected from light.

PACKS

— R/C vial containing 200 units of lyophilised Factors II, IX, and X
— R/C vial containing 10 ml of Water for Injections B.P.
— Kit for reconstitution and injection
— R/C vial containing 500 units of lyophilised Factors II, IX, and X
— R/C vial containing 10 ml of Water for Injections B.P.
— Kit for reconstitution and injection
— R/C vial containing 1000 units of lyophilised Factors II, IX, and X
— R/C vial containing 20 ml of Water for Injections B.P.
— Kit for reconstitution and injection

REFERENCES

1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6: 110 — 116 (1968)
3. FISCHER M., DEUTSCH E.: Therapie der Hämophilien. Dtsch. med. J. No. 14: 499 — 505 (1968)
4. JOSSO F., MENACHE D., STEINBUCH M., BLATRIX C., SOULIER J.P.: The P.P.S.B. Fraction. Bibl. haemat. No. 34: pp. 18 — 22 (1970)
5. LANDBECK G.: Störungen der Hämostase. In Lawin P.: Praxis der Intensivbehandlung. Thieme, Stuttgart (1971)
6. LANDBECK G.: Substitutionstherapie mit Faktor VIII und IX Präparaten. In Pettenkofer H.: Gezielte Therapie mit Blutbestandteilen. Lehmanns Verlag, München (1968)
7. LOELIGER E.A., HENSEN A.: Substitution Therapy in Haemophilia B. Thrombos. Diathes. Haemorrh. 6, 391 (1961)
8. SOULIER J.P., STEINBUCH M.: Über die Herstellung und klinische Anwendung von Gerinnungsfaktoren-Konzentraten aus menschlichem Plasma. Z. Ges. Med. 20: 311 (1965)
9. TULLIS J., BREEN F.A.: Christmas Factor Concentrates. The Clinical Use of Several Preparations. Bibl. haemat. No. 34: pp. 40 — 51 (1970)

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Production Division of
IMMUNO AG Vienna Austria

6205911EA10/5-2

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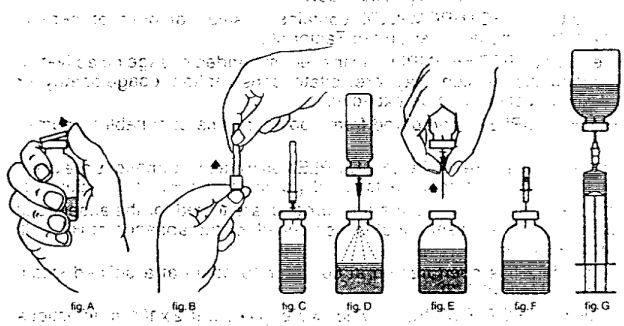
1. Warm the unopened bottle containing the solvent to room temperature (max. 37°C).
2. Remove the caps from the concentrate and solvent bottles (fig. A) and disinfect the rubber stoppers of both bottles.
3. The enclosed transfer needle (double-ended needle) is protected by 2 plastic caps sealed by a weld mark. Break the weld (fig. B) 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 (maximum rate of injection: 1 ml/min.) inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Haemophilia B is given in the dosage guide below.

Dosage guide for the treatment of severe and semi-severe cases of Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:

One unit of Factor IX/kg body weight = 1% increase of Factor IX in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg body weight	Maintenance dose at intervals of 6 to 12 (24) hrs. in units Factor IX per kg body weight
A) Surface bleeding of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleeding following injuries Uncomplicated dental extractions	5—10%	15 U	7—15 U
B) Severe muscle haematoma Moderate bleeding following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleeding Haematuria Complicated dental extractions Minor surgery	15—30%	20—30 U	15—30 U
C) Major surgery	more than 50%	75 U	50—75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in vivo half-life of Factor IX, which is approx. 12—30 hours, a successful result will be achieved by repeated administration of PROTHROMPLEX at intervals of 6—12 hours. To assure absolute control of treatment, determination of the PTT should be made and where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein a high concentration of coagulation Factor IX is reached in the circulation. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), PROTHROMPLEX should not be administered unless consumption of the coagulation factors has been previously interrupted with Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX though the following reactions may occur:

1. Allergic Reactions

   All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once. Allergic reactions should be controlled with antihistamines and routine shock-treatment given for anaphylactic

620549NEA06

Prothromplex® TIM 4
Partial Prothrombin Complex (Human) heat-treated

P.O.M

Product Licence Nos. 0215/0006/7/8

PROTHROMPLEX TIM 4 contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

PROTHROMPLEX TIM 4 is prepared from pooled plasma of suitable* human donors and freeze-dried for stability in storage.
Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit** of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.
To eliminate the potential risk of thrombogenic complications associated with Factor IX preparations PROTHROMPLEX TIM 4 is routinely tested for the absence of activated coagulation factors.
In addition, PROTHROMPLEX TIM 4 contains a small amount of heparin (0.1 i.u.*** heparin per unit of Factor II).
When using PROTHROMPLEX TIM 4 in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboembolism is to be expected.
To decrease the potential risk of transmission of viral infections the following steps are taken:

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

INDICATIONS

Treatment of cases of haemophilia B (lack of Factor IX).
By administering an appropriate dose of PROTHROMPLEX TIM 4, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma.
The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).
The most reliable results are obtained by quantitative activity assays of Factor IX.

ADMINISTRATION

Directions for Reconstitution of the Solution for Injection

The lyophilised PROTHROMPLEX TIM 4 must be dissolved immediately before injection using the amount of solvent provided (10 ml).

Directions for use

1. Warm the PROTHROMPLEX TIM 4 and solvent bottles to approx. 37°C.

* Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.

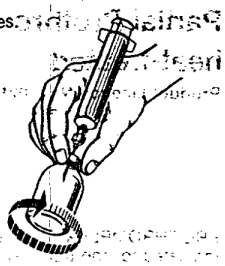
** One unit Factor II, IX and X is equivalent to the Factor II, IX and X activity present in 1 ml of average fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

*** 1 i.u. heparin according to WHO standard.

2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures.

A) a) Fit a disposable needle onto a syringe of suitable size.

b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe; remove the needle from the syringe.



c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.

d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2—3 min.).

e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) 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.

b) Remove the solvent bottle **with the transfer needle** from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.

c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.

d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

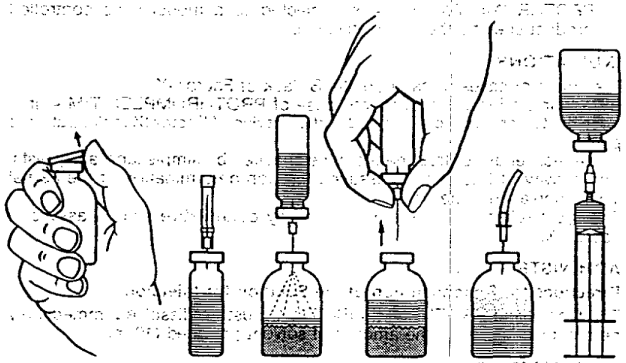


fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. 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 1 ml/min.

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLE TIM 4. It is dependent upon the severity of the coagulation defect and th degree of the traumatic and haemorrhagic tissue damage. The suggeste dosage for the treatment of Haemophilia B is given in the dosage guic below.

Dosage guide for the treatment of severe and semi-severe cases Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:

One unit of Factor IX/kg body weight = 1% increase of Factor I in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dos at intervals of: 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5—10%	15 U	7—15 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions Minor surgery	15—30%	20—30 U	15—30 U
C) Major surgery	more than 50%	75 U	50—75 U

It is suggested that a high initial dosage be chosen to ensure a rapi and sufficient increase of Factor IX thus achieving a reliable cessation c bleeding. Here, as well as with the subsequent maintenance therap the initially short half-life of the coagulation factors has to be considered Depending on the in vivo half-life of Factor IX, which is approx. 12—30 hours a successful result will be achieved by repeated administration of PRO THROMPLEX TIM 4 at intervals of 6—12 hours. To assure absolute contro of treatment, determination of the PTT should be made and where possible quantitative assays of Factor IX activity. Treatment should be maintaine up to the resorption of the tissue haemorrhage or until the wounds hav healed completely, thus ensuring a complication-free postoperativ course. The special advantage of PROTHROMPLEX TIM 4 lies in the fac that by application of small volumes of fluid and a slight amount of protein high concentration of coagulation Factor IX is reached in the circulation The danger of volume or protein overloading of the patient is avoided ever with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulatio (DIC), PROTHROMPLEX TIM 4 should not be administered unless consumption of the coagulation factors has been previously interrupte with Heparin.

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SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 4 though the following reactions may occur:

1. Allergic Reactions
All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 4 must be interrupted at once. Allergic reactions should be controlled with antihistamines and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.
3. Despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out.

CONTRA-INDICATIONS

Despite the precautions taken in the checking of donors, donations and the final product, and the introduction of a thermoinactivation procedure, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using PROTHROMPLEX TIM 4 to control haemorrhage in non-life-saving situations in liver disease patients and those undergoing anticoagulant therapy.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6°C, protected from light.

PACKS

of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container.

1 R/C bottle containing lyophilized PROTHROMPLEX TIM 4
1 R/C bottle containing 10 ml Water for Injections, B.P.
1 Kit for reconstitution and injection.

REFERENCES

1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6, 110:116 (1968)
3. FISCHER M., DEUTSCH E.: Therapie der Hämophilien. Dtsch.med.J. No. 14, 499:505 (1968)
4. JOSSO F., MENACHE D., STEINBUCH M., BLATRIX C., SOULIER J.P.: The P.P.S.B. Fraction. Bibl. haemat. No. 34, pp. 18:22 (1970)
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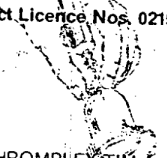
Prothromplex® TIM 4

Partial Prothrombin Complex (Human) heat-treated

P.O.M.

Product Licence Nos. 0215/0006/7/8



PROTHROMPLEX TIM 4 contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

PROTHROMPLEX TIM 4 is prepared from pooled plasma of suitable* human donors and freeze-dried for stability in storage.
Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit** of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.
To eliminate the potential risk of thrombogenic complications associated with Factor IX preparations PROTHROMPLEX TIM 4 is routinely tested for the absence of activated coagulation factors.
In addition, PROTHROMPLEX TIM 4 contains a small amount of heparin (0.1 i.u.*** heparin per unit of Factor II).
When using PROTHROMPLEX TIM 4 in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboembolism is to be expected.
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 PROTHROMPLEX TIM 4 and the final product were tested for HB_S-antigen by Radio Immune Assay (RIA) and found non-reactive.
2. Thermoinactivation by Method TIM 4:
   PROTHROMPLEX TIM 4 is subjected to a model virus controlled product specific thermoinactivation.

INDICATIONS

Treatment of cases of haemophilia B (lack of Factor IX).
By administering an appropriate dose of PROTHROMPLEX TIM 4, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma.
The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).
The most reliable results are obtained by quantitative activity assays of Factor IX.

ADMINISTRATION

Directions for Reconstitution of the Solution for Injection

The lyophilised PROTHROMPLEX TIM 4 must be dissolved immediately before injection using the amount of solvent provided (10 ml).

Directions for use

1. Warm the PROTHROMPLEX TIM 4 and solvent bottles to approx. 37°C.

* Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.

** One unit Factor II, IX and X is equivalent to the Factor II, IX and X activity present in 1 ml of average fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

*** 1 i.u. heparin according to WHO standard.

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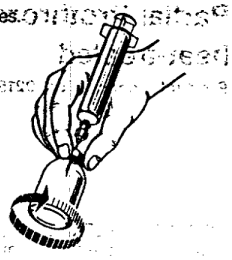
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures:



A) a) Fit a disposable needle onto a syringe of suitable size.
   b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe; remove the needle from the syringe.
   c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.
   d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2—3 min.).
   e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) 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.
   b) Remove the solvent bottle **with the transfer needle** from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.
   c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.
   d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

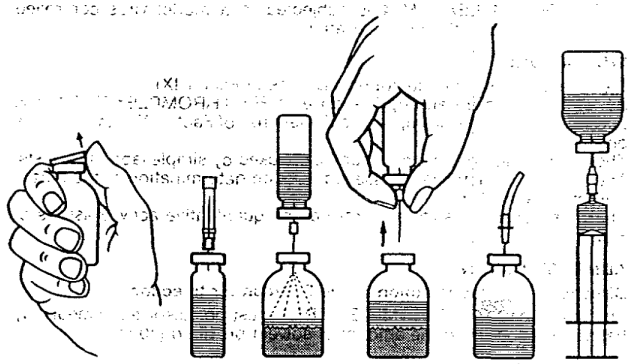


fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. 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 1 ml/min.

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX TIM 4. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Haemophilia B is given in the dosage guide below.

Dosage guide for the treatment of severe and semi-severe cases of Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:

One unit of Factor IX/kg body weight = 1% increase of Factor IX in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dose at intervals of 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5—10%	15 U	7—15 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions Minor surgery	15—30%	20—30 U	15—30 U
C) Major surgery	more than 50%	75 U	50—75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in vivo half-life of Factor IX, which is approx. 12—30 hours, a successful result will be achieved by repeated administration of PROTHROMPLEX TIM 4 at intervals of 6—12 hours. To assure absolute control of treatment, determination of the PTT should be made and where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX TIM 4 lies in the fact that by application of small volumes of fluid and a slight amount of protein a high concentration of coagulation Factor IX is reached in the circulation. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), PROTHROMPLEX TIM 4 should not be administered unless consumption of the coagulation factors has been previously interrupted with Heparin.

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SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 4 though the following reactions may occur:

1. Allergic Reactions:
   All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 4 must be interrupted at once. Allergic reactions should be controlled with antihistamines and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and /or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.
3. Despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out.

CONTRA-INDICATIONS

Despite the precautions taken in the checking of donors, donations and the final product, and the introduction of a thermoinactivation procedure, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using PROTHROMPLEX TIM 4 to control haemorrhage in non-life-saving situations in liver disease patients and those undergoing anticoagulant therapy.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6°C. protected from light.

PACKS

of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container.

1 R/C bottle containing lyophilized PROTHROMPLEX TIM 4
1 R/C bottle containing 10 ml Water for Injections, B.P.
1 Kit for reconstitution and injection

REFERENCES

1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6, 110-116 (1968)
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Partial Prothrombin Complex (Human)

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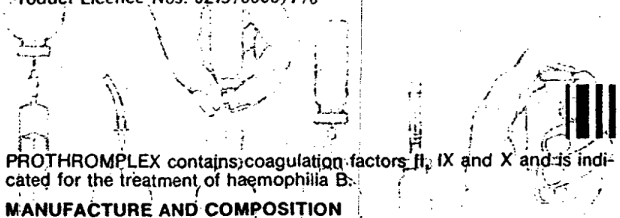


PROTHROMPLEX contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

PROTHROMPLEX is prepared from pooled plasma of suitable* human donors and freeze-dried for stability in storage. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for their GPT level and the absence of HB_S-antigen. Any donor who has a history of a pathological transaminase level or a positive HB_S-antigen test, is permanently excluded from the donor programme. Each batch of the final product is tested for absence of HB_S-antigen as well as to discount the likelihood of provoking disseminated intravascular coagulation. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out.

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit** of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.

INDICATIONS

Treatment of cases of haemophilia B (lack of Factor IX).
By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma. The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).
The most reliable results are obtained by quantitative activity assays of Factor IX.

ADMINISTRATION

Directions for Reconstitution of the Solution for Injection

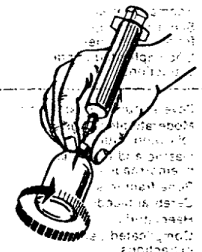
The lyophilised PROTHROMPLEX must be dissolved immediately before injection using the amount of solvent provided (10 ml).

Directions for use

1. Warm the PROTHROMPLEX and solvent bottles to approx. 37° C.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures.

A) a) Fit a disposable needle onto a syringe of suitable size.

b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe; remove the needle from the syringe.



c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.

d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2-3 min.).

e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) 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.

b) Remove the solvent bottle with the transfer needle from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.

c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.

d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

* Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.

** One unit Factor II, IX and X is equivalent to the Factor II, IX and X activity present in 1 ml of average fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX, Human, 72/32

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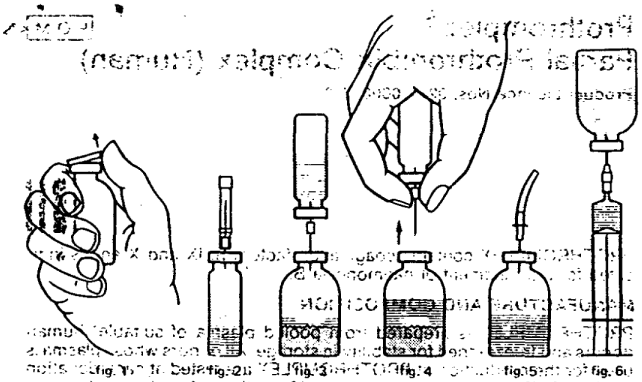

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. 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 1 ml/min.

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Haemophilia B is given in the dosage guide below.

Dosage guide for the treatment of severe and semi-severe cases of Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:
One unit of Factor IX/kg body weight = 1% increase of Factor IX in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dose at intervals of 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5-10%	15 U	7-15 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions Minor surgery	15-30%	20-30 U	15-30 U
C) Major surgery	more than 50%	75 U	50-75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in vivo half-life of Factor IX, which is approx. 12-30 hours, a successful result will be achieved by repeated administration of PROTHROMPLEX at intervals of 6-12 hours. To assure absolute control of treatment, determination of the PTT should be made and where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein a high concentration of coagulation Factor IX is reached in the circulation. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), PROTHROMPLEX should not be administered unless consumption of the coagulation factors has been previously interrupted with Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once. Allergic reactions should be controlled with antihistamines and glucocorticoids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. Despite the precautions taken, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.

CONTRA-INDICATIONS

Despite the precautions taken in the checking of donors, donations and the final product, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using PROTHROMPLEX to control haemorrhage in non-life-saving situations in liver disease patients and those undergoing anticoagulant therapy.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6° C, protected from light.

PACKS

of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container.

1 R/C bottle containing lyophilized PROTHROMPLEX
1 R/C bottle containing 10 ml Water for Injections, B.P.
1 Kit for reconstitution and injection

REFERENCES

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9. *TULLIS J., BREEN F.A.: Christmas Factor Concentrates.* The Clinical Use of Several Preparations. Bibl. haemat. No. 34, pp. 40:51 (1970)

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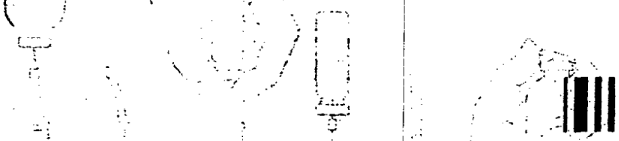


PROTHROMPLEX contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

PROTHROMPLEX is prepared from pooled plasma of suitable* human donors and freeze-dried for stability in storage. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for their GPT level and the absence of HB_s-antigen. Any donor who has a history of a pathological transaminase level or a positive HB_s-antigen test, is permanently excluded from the donor programme. Each batch of the final product is tested for absence of HB_s-antigen as well as to discount the likelihood of provoking disseminated intravascular coagulation. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out.

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit** of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.

INDICATIONS

Treatment of cases of haemophilia B (lack of Factor IX).
By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma.
The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).
The most reliable results are obtained by quantitative activity assays of Factor IX.

ADMINISTRATION

Directions for Reconstitution of the Solution for Injection

The lyophilised PROTHROMPLEX must be dissolved immediately before injection using the amount of solvent provided (10 ml).

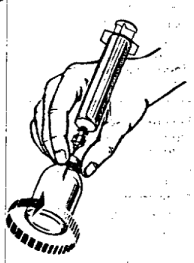
Directions for use

1. Warm the PROTHROMPLEX and solvent bottles to approx. 37° C.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures.

A) a) Fit a disposable needle onto a syringe of suitable size.

b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe; remove the needle from the syringe.

c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.



d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2-3 min.).

e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) 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.

b) Remove the solvent bottle **with the transfer needle** from the lyophilisate bottle (fig. 4). **Gently agitate the latter in order to accelerate solution.**

c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.

d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

* Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.

** One unit Factor II, IX and X is equivalent to the Factor II, IX and X activity present in 1 ml of average fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

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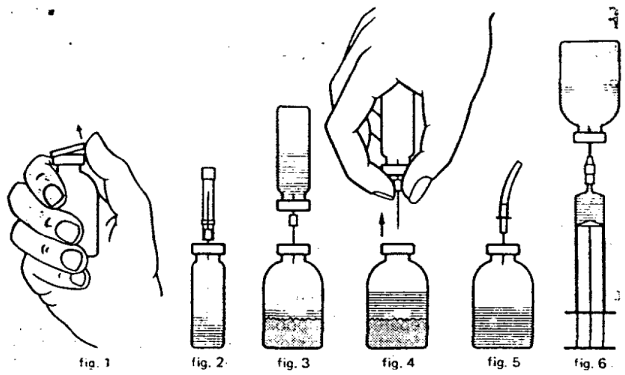

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. 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 1 ml/min.

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Haemophilia B is given in the dosage guide below.

Dosage guide for the treatment of severe and semi-severe cases of Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:
One unit of Factor IX/kg body weight = 1% increase of Factor IX in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dose at intervals of 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5-10%	15 U	7-15 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions Minor surgery	15-30%	20-30 U	15-30 U
C) Major surgery	more than 50%	75 U	50-75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in vivo half-life of Factor IX, which is approx. 12-30 hours, a successful result will be achieved by repeated administration of PROTHROMPLEX at intervals of 6-12 hours. To assure absolute control of treatment, determination of the PTT should be made and where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein a high concentration of coagulation Factor IX is reached in the circulation. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), PROTHROMPLEX should not be administered unless consumption of the coagulation factors has been previously interrupted with Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once. Allergic reactions should be controlled with antihistamines and glucocorticoids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. Despite the precautions taken, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.

CONTRA-INDICATIONS

Despite the precautions taken in the checking of donors, donations and the final product, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using PROTHROMPLEX to control haemorrhage in non-life-saving situations in liver disease patients and those undergoing anticoagulant therapy.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6° C, protected from light.

PACKS

of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container.
1 R/C bottle containing lyophilized PROTHROMPLEX
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PROTHROMPLEX contains coagulation factors II, IX and X and is indicated for the treatment of haemophilia B.

MANUFACTURE AND COMPOSITION

PROTHROMPLEX is prepared from pooled plasma of suitable* human donors and freeze-dried for stability in storage. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for their GPT level and the absence of HB_S-antigen. Any donor who has a history of a pathological transaminase level or a positive HB_S-antigen test, is permanently excluded from the donor programme. Each batch of the final product is tested for absence of HB_S-antigen as well as to discount the likelihood of provoking disseminated intravascular coagulation. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out.

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor IX as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit** of Factor IX. Despite a moderate total protein content a high concentration of Factor II and X is also reached.

INDICATIONS

Treatment of cases of haemophilia B (lack of Factor IX).

By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma. The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT).

The most reliable results are obtained by quantitative activity assays of Factor IX.

ADMINISTRATION

Directions for Reconstitution of the Solution for Injection

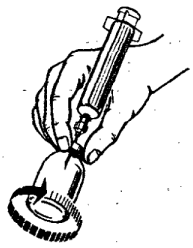
The lyophilised PROTHROMPLEX must be dissolved immediately before injection using the amount of solvent provided (10 ml).

Directions for use

1. Warm the PROTHROMPLEX and solvent bottles to approx. 37° C.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures.

A) a) Fit a disposable needle onto a syringe of suitable size.

b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe; remove the needle from the syringe.



c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.

d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2-3 min.).

e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) 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.

b) Remove the solvent bottle **with the transfer needle** from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.

c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.

d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

* Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.

** One unit Factor II, IX and X is equivalent to the Factor II, IX and X activity present in 1 ml of average fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

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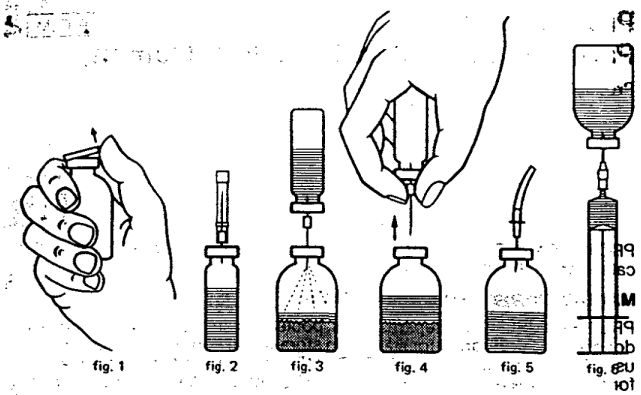

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. 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 1 ml/min.

Do not exceed the maximum injection rate of 1 ml/min.

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Haemophilia B is given in the dosage guide below.

Dosage guide for the treatment of severe and semi-severe cases of Haemophilia B:

Formula for the calculation of the necessary quantity of Factor IX:
One unit of Factor IX/kg body weight = 1% increase of Factor IX in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dose at intervals of 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5-10%	15 U	7-15 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions Minor surgery	15-30%	20-30 U	15-30 U
C) Major surgery	more than 50%	75 U	50-75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in vivo half-life of Factor IX, which is approx. 12-30 hours, a successful result will be achieved by repeated administration of PROTHROMPLEX at intervals of 6-12 hours. To assure absolute control of treatment, determination of the PTT should be made and where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein a high concentration of coagulation Factor IX is reached in the circulation. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), PROTHROMPLEX should not be administered unless consumption of the coagulation factors has been previously interrupted with Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once. Allergic reactions should be controlled with antihistamines and glucocorticoids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. Despite the precautions taken, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor antibody is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.

CONTRA-INDICATIONS

Despite the precautions taken in the checking of donors, donations and the final product, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using PROTHROMPLEX to control haemorrhage in non-life-saving situations in liver disease patients and those undergoing anticoagulant therapy.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +6° C, protected from light.

PACKS

of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container.
1 R/C bottle containing lyophilized PROTHROMPLEX
1 R/C bottle containing 10 ml Water for Injections, B.P.
1 Kit for reconstitution and injection

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1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6, 110:116 (1968)
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NEUTRAL ENGLISH TEXTS

PROTHROMPLEX
BEBULIN

6205212 EW03

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 4 though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarious rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 4 must be interrupted at once.

   Allergic reactions should be controlled with antihistamines and glucocorticosteroids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of glucocorticosteroids or immunosuppressive substances has hardly influenced the formation of inhibitors.

In all probability the risk of transmission of viral hepatitis is eliminated by careful donor and plasma selection and product specific steam treatment.

The transmission of HIV will be prevented by the above measures.

SHELF LIFE AND STORAGE

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

PACKS

Each containing the equivalent of 200 units or 500 units of Factor II, Factor IX and Factor X

1 R/C bottle containing lyophilised PROTHROMPLEX TIM 4
1 R/C bottle containing 20 ml of Aqua ad Iniectabilia
1 kit for reconstitution and injection

REFERENCES

1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6: 110 — 116 (1968)
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PROTHROMPLEX® TIM 4

Partial Prothrombin Complex (Human)

Steam Treated

Prothrombin Complex is understood to include the vitamin K, dependent coagulation Factors II, VII, IX and X.

PROTHROMPLEX TIM 4 contains coagulation Factors II, IX and X and is indicated for the treatment of all coagulation disorders due to lack of Factor II (Prothrombin), Factor IX (Christmas Factor), and Factor X (Stuart-Prower Factor).

MANUFACTURE AND COMPOSITION

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 50-fold concentration of Factor II as compared to fresh plasma. Despite a moderate total protein content a high concentration of Factors IX and X is also reached. PROTHROMPLEX TIM 4 is distributed in packs containing either 500 or 200 units* of Factors II, IX and X.

PROTHROMPLEX 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 PROTHROMPLEX TIM 4 only plasma units are used which are non-reactive in tests for HB_S-antigen and HIV-antibodies.

To further reduce the potential risk of viral transmission the manufacture of PROTHROMPLEX TIM 4 includes a product specific steam treatment (Steam Treatment Immuno 4). Samples of PROTHROMPLEX TIM 4, which were spiked with 2×10^6 infectious units of HIV/ml, did not contain any detectable infectious virus after the product specific steam treatment.

INDICATIONS

Indications for PROTHROMPLEX TIM 4 include all types of haemorrhages caused by inherited or acquired coagulation disorders due to reduced Factor II, IX and/or X activity.

Treatment for inherited or congenital coagulation disorders

1. Hypo- or A-prothrombinaemia (Factor II deficiency)
2. Haemophilia B (Factor IX deficiency)
3. Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency)
4. Stuart-Prower Factor deficiency (Factor X deficiency)
5. Combined deficiency of Factors II, IX or X.

Treatment for acquired coagulation disorders

1. Haemorrhages due to a deficiency of Factors II, IX and X with severe damage of the liver parenchyma (hepatitis, cirrhosis of the liver, severe toxic liver damage through poisoning etc.).
2. Emergency treatment of severe acute haemorrhages which may occur during anticoagulant therapy. This is of especial use if anticoagulants are administered during the last three months of pregnancy. PROTHROMPLEX TIM 4 normalizes Factor II, IX and X activity.

* 1 I.U. Factor IX (according to WHO standard), 1 unit Factor II and X correspond to the activity of Factors II, IX and X respectively, in 1 ml of fresh average human plasma.

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3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROMPLEX TIM 4, Factor II, IX and X activity is normalized.
4. Severe acute haemorrhages caused by vitamin K deficiency (genuine vitamin K deficiency or as (for example) a consequence of resorption disturbances). Through the administration of PROTHROMPLEX TIM 4, Factor II, IX and X activity is normalized.
5. Before carrying out biopsies or pre-operative treatment of patients with Factor II, IX or X deficiencies.

By administering an appropriate dose of PROTHROMPLEX TIM 4, it is possible to achieve a prompt and sufficient rise of Factors II, IX and X in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factors II and X is determined by the Thromboplastin Time (Quick value), the Thrombotest or Normotest. The activity of Factor IX is obtained from the results of the Partial Thromboplastin Time (PTT).

The most reliable results are reached through quantitative assays on the activity of each of the Factors II, IX and X.

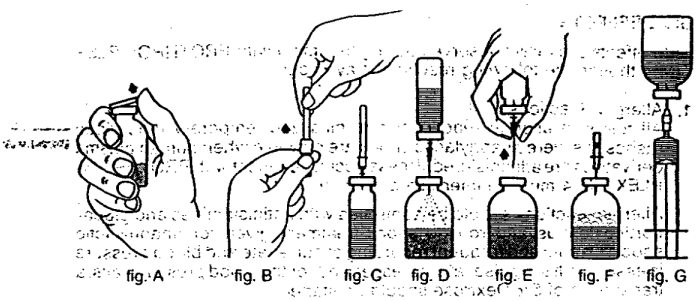
In acquired coagulation disorders which involve reduction of Factors II, VII, IX and X, the administration of vitamin K_1 is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K_1 in contrast to PROTHROMPLEX TIM 4 becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K_1 is no longer recommended because of occasional side-effects, it must be taken into consideration that by parenteral but not intravenous administration, a further delay in effectiveness will occur.

Reduction of the coagulation Factors VII and V, which may be involved in the above mentioned coagulation disorders, is not sufficiently influenced by PROTHROMPLEX TIM 4. ANTIHAEMOPHILIC PLASMA HUMAN "HAEMODERIVATE" (AHP) is recommended as a supplement.

RECONSTITUTION OF CONCENTRATE

PROTHROMPLEX TIM 4 is to be stored in lyophilised condition and should only be reconstituted immediately before administration. The solution must then be used promptly. Entered vials must not be reused.

1. Warm the unopened bottle containing 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 covers sealed by a weld mark. Break the weld (Fig. B) by twisting the covers. Remove the outer cover and insert the exposed needle into the rubber stopper of the solvent bottle (Fig. C).
4. Remove the inner cover 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). 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

1. 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).
2. Disconnect the filter needle from the syringe and slowly (maximum rate of injection: 2 ml/min) inject the solution intravenously with the enclosed disposable intravenous needle (or the infusion set with a winged adapter).

If any other kit for reconstitution and administration than that enclosed is used, make sure that this kit contains an adequate filter.

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX TIM 4. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage.

In cases of inherited or congenital coagulation disorders high initial dosage is recommended in order to ensure a rapid and sufficient rise in the coagulation factors concerned and thus achieve a reliable cessation of bleeding. Here, as well as with the following maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of the factors (Factor II approx. 40 — 60 hours, Factor IX approx. 12 — 30 hours, Factor X approx. 20 — 60 hours) successful results are achieved by repeated administration of PROTHROMPLEX TIM 4 at intervals of 12 — 24 hours. To assure absolute control of treatment, the blood coagulation should be tested as far as possible with quantitative activity assays of each of the coagulation factors. Treatment should be rigidly maintained up to complete healing of the wounds, especially in cases of inherited coagulation disorders, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX TIM 4 lies in the fact that by application of small volumes of fluid and a slight amount of protein, a high concentration of coagulation factors (II, IX and X) is reached in the circulation. The danger of a volume or protein overloading of the patient is excluded even with the administration of higher doses.

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or splenoportography. They should previously receive sufficient PROTHROMPLEX TIM 4 to hold their Thromboplastin Time or Normotest value above 50% for several days.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), administration of PROTHROMPLEX TIM 4 should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

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SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 4 though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarious rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 4 must be interrupted at once.

   Allergic reactions should be controlled with antihistamines and glucocorticosteroids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of glucocorticosteroids or immunosuppressive substances has hardly influenced the formation of inhibitors.

The risk of transmission of viral hepatitis is eliminated with high probability by careful donor and plasma selection and product specific steam treatment.

The transmission of HTLV-III can be prevented by above measures.

SHELF LIFE AND STORAGE

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

PACKS

Each containing the equivalent of 200 units or 500 units of Factor II, Factor IX and Factor X

1 R/C bottle containing lyophilized PROTHROMPLEX TIM 4
1 R/C bottle containing 20 ml of Aqua ad Iniectabilia
1 kit for reconstitution and injection

REFERENCES

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PROTHROMPLEX® TIM 4

Partial Prothrombin Complex (Human)

Steam Treated

Prothrombin Complex is understood to include the vitamin K, dependent coagulation Factors II, VII, IX and X.

PROTHROMPLEX TIM 4 contains coagulation Factors II, IX and X and is indicated for the treatment of all coagulation disorders due to lack of Factor II (Prothrombin), Factor IX (Christmas Factor), and Factor X *(Stuart-Prower Factor).*

MANUFACTURE AND COMPOSITION

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 50-fold concentration of Factor II as compared to fresh plasma. Despite a moderate total protein content a high concentration of Factors IX and X is also reached. PROTHROMPLEX TIM 4 is distributed in packs containing either 500 or 200 units* of Factors II, IX and X.

PROTHROMPLEX TIM 4 is prepared from pooled human plasma.

All plasma units are exclusively obtained from Central Europe and the United States of America. The criteria for admission of each donor and the performance of each plasmapheresis are at least as rigorous as the respective national laws and regulations in the country of origin.

For the manufacture of PROTHROMPLEX TIM 4 only plasma units are used which are non-reactive in tests for HB_s-antigen and HTLV-III-antibodies.

To inactivate potentially present viral agents the manufacture of PROTHROMPLEX TIM 4 includes a product specific steam treatment (Steam Treatment Immuno 4). Samples of PROTHROMPLEX TIM 4, which were spiked with 2×10^6 infectious units of HTLV-III/ml, did not contain any detectable infectious virus after the product specific steam treatment. The HTLV-III titre was determined after incubation with HT-H9 cells and subsequent measurement of reverse transcriptase activity in the clarified cell supernatant.

INDICATIONS

Indications for PROTHROMPLEX TIM 4 include all types of haemorrhages caused by inherited or acquired coagulation disorders due to reduced Factor II, IX and/or X activity.

Treatment for inherited or congenital coagulation disorders

1. Hypo- or A-prothrombinaemia (Factor II deficiency)
2. Haemophilia B (Factor IX deficiency)
3. Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency)
4. Stuart-Prower Factor deficiency (Factor X deficiency)
5. Combined deficiency of Factors II, IX or X.

Treatment for acquired coagulation disorders

1. Haemorrhages due to a deficiency of Factors II, IX and X with severe damage of the liver parenchyma (hepatitis, cirrhosis of the liver, severe toxic liver damage through poisoning etc.).
2. Emergency treatment of severe acute haemorrhages which may occur during anticoagulant therapy. This is of especial use if anticoagulants are administered during the last three months of pregnancy. PROTHROMPLEX TIM 4 *normalizes* Factor II, IX and X activity.

* 1 I.U. Factor IX (according to WHO standard), 1 unit Factor II and X correspond to the activity of Factors II, IX and X respectively, in 1 ml of fresh average human plasma.

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3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROMPLEX TIM 4, Factor II, IX and X activity is normalized.
4. Severe acute haemorrhages caused by vitamin K deficiency (genuine vitamin K deficiency or as (for example) a consequence of resorption disturbances). Through the administration of PROTHROMPLEX TIM 4, Factor II, IX and X activity is normalized.
5. Before carrying out biopsies or pre-operative treatment of patients with Factor II, IX or X deficiencies.

By administering an appropriate dose of PROTHROMPLEX TIM 4, it is possible to achieve a prompt and sufficient rise of Factors II, IX and X in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factors II and X is determined by the Thromboplastin Time (Quick value), the Thrombotest or Normotest. The activity of Factor IX is obtained from the results of the Partial Thromboplastin Time (PTT).

The most reliable results are reached through quantitative assays on the activity of each of the Factors II, IX and X.

In acquired coagulation disorders which involve reduction of Factors II, VII, IX and X, the administration of vitamin K_1 is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K_1 in contrast to PROTHROMPLEX TIM 4 becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K_1 is no longer recommended because of occasional side-effects, it must be taken into consideration that by parenteral but not intravenous administration, a further delay in effectiveness will occur.

Reduction of the coagulation Factors VII and V, which may be involved in the above mentioned coagulation disorders, is not sufficiently influenced by PROTHROMPLEX TIM 4. ANTIHAEMOPHILIC PLASMA HUMAN "HAEMODERIVATE" (AHP) is recommended as a supplement.

RECONSTITUTION OF CONCENTRATE

PROTHROMPLEX TIM 4 is to be stored in lyophilised condition and should only be reconstituted immediately before administration. The solution must then be used promptly. Entered vials must not be reused.

1. Warm the unopened bottle containing 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 covers sealed by a weld mark. Break the weld (Fig. B) by twisting the covers. Remove the outer cover and insert the exposed needle into the rubber stopper of the solvent bottle (Fig. C).
4. Remove the inner cover 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). 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.

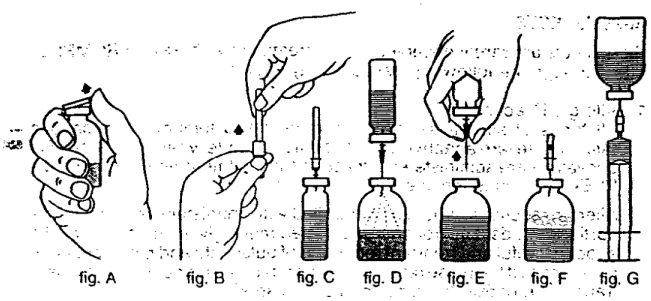

fig. A fig. B fig. C fig. D fig. E fig. F fig. G

ADMINISTRATION

1. 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).
2. Disconnect the filter needle from the syringe and slowly (maximum rate of injection: 2 ml/min) inject the solution intravenously with the enclosed disposable intravenous needle (or the infusion set with a winged adapter).

If any other kit for reconstitution and administration than that enclosed is used, make sure that this kit contains an adequate filter.

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX TIM 4. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage.

In cases of inherited or congenital coagulation disorders high initial dosage is recommended in order to ensure a rapid and sufficient rise in the coagulation factors concerned and thus achieve a reliable cessation of bleeding. Here, as well as with the following maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of the factors (Factor II approx. 40 — 60 hours, Factor IX approx. 12 — 30 hours, Factor X approx. 20 — 60 hours) successful results are achieved by repeated administration of PROTHROMPLEX TIM 4 at intervals of 12 — 24 hours. To assure absolute control of treatment, the blood coagulation should be tested as far as possible with quantitative activity assays of each of the coagulation factors. Treatment should be rigidly maintained up to complete healing of the wounds, especially in cases of inherited coagulation disorders, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX TIM 4 lies in the fact that by application of small volumes of fluid and a slight amount of protein, a high concentration of coagulation factors (II, IX and X) is reached in the circulation. The danger of a volume or protein overloading of the patient is excluded even with the administration of higher doses.

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or splenoportography. They should previously receive sufficient PROTHROMPLEX TIM 4 to hold their Thromboplastin Time or Normotest value above 50% for several days.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), administration of PROTHROMPLEX TIM 4 should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

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SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 2 though the following reactions may occur:

1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarious rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 2 must be interrupted at once.

   Allergic reactions should be controlled with antihistamines and glucocorticosteroids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.

2. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of glucocorticosteroids or immunosuppressive substances has hardly influenced the formation of inhibitors.

The risk of transmission of viral hepatitis is eliminated with high probability by careful donor and plasma selection and product specific steam treatment.

The transmission of HTLV-III can be prevented by above measures.

SHELF LIFE AND STORAGE

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

PACKS

Each containing the equivalent of 200 units or 500 units of Factor II, Factor IX and Factor X

1 R/C bottle containing lyophilized PROTHROMPLEX TIM 2
1 R/C bottle containing 20 ml of Aqua ad Iniectabilia
1 kit for reconstitution and injection

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1. BIGGS R., MACFARLANE R. G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
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PROTHROMPLEX® TIM 2

Partial Prothrombin Complex (Human)

Steam Treated

Prothrombin Complex is understood to include the vitamin K_1 dependent coagulation Factors II, VII, IX and X.

PROTHROMPLEX TIM 2 contains coagulation Factors II, IX and X and is indicated for the treatment of all coagulation disorders due to lack of Factor II (Prothrombin), Factor IX (Christmas Factor), and Factor X (Stuart-Prower Factor).

MANUFACTURE AND COMPOSITION

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 50-fold concentration of Factor II as compared to fresh plasma. Despite a moderate total protein content a high concentration of Factors IX and X is also reached. PROTHROMPLEX TIM 2 is distributed in packs containing either 500 or 200 units* of Factors II, IX and X.

PROTHROMPLEX TIM 2 is prepared from pooled human plasma.

All plasma units are exclusively obtained from Central Europe and the United States of America. The criteria for admission of each donor and the performance of each plasmapheresis are at least as rigorous as the respective national laws and regulations in the country of origin.

For the manufacture of PROTHROMPLEX TIM 2 only plasma units are used which are non-reactive in tests for HB_S-antigen and HTLV-III-antibodies.

To inactivate potentially present viral agents the manufacture of PROTHROMPLEX TIM 2 includes a product specific steam treatment (Steam Treatment Immuno 2). Samples of PROTHROMPLEX TIM 2, which were spiked with 2×10^6 infectious units of HTLV-III/ml, did not contain any detectable infectious virus after the product specific steam treatment. The HTLV-III titre was determined after incubation with HT-H9 cells and subsequent measurement of reverse transcriptase activity in the clarified cell supernatant.

INDICATIONS

Indications for PROTHROMPLEX TIM 2 include all types of haemorrhages caused by inherited or acquired coagulation disorders due to reduced Factor II, IX and/or X activity.

Treatment for inherited or congenital coagulation disorders:

1. Hypo- or A-prothrombinaemia (Factor II deficiency)
2. Haemophilia B (Factor IX deficiency)
3. Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency)
4. Stuart-Prower Factor deficiency (Factor X deficiency)
5. Combined deficiency of Factors II, IX or X.

Treatment for acquired coagulation disorders

1. Haemorrhages due to a deficiency of Factors II, IX and X with severe damage of the liver parenchyma (hepatitis, cirrhosis of the liver, severe toxic liver damage through poisoning etc.).
2. Emergency treatment of severe acute haemorrhages which may occur during anticoagulant therapy. This is of especial use if anticoagulants are administered during the last three months of pregnancy. PROTHROMPLEX TIM 2 normalizes Factor II, IX and X activity.

* 1 I.U. Factor IX (according to WHO standard), 1 unit Factors II and X correspond to the activity of Factor II, IX and X respectively, in 1 ml of fresh average human plasma.

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3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROMPLEX TIM 2, Factor II, IX and X activity is normalized.
4. Severe acute haemorrhages caused by vitamin K deficiency (genuine vitamin K deficiency or as (for example) a consequence of resorption disturbances). Through the administration of PROTHROMPLEX TIM 2, Factor II, IX and X activity is normalized.
5. Before carrying out biopsies or pre-operative treatment of patients with Factor II, IX or X deficiencies.

By administering an appropriate dose of PROTHROMPLEX TIM 2, it is possible to achieve a prompt and sufficient rise of Factors II, IX and X in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factors II and X is determined by the Thromboplastin Time (Quick value), the Thrombotest or Normotest. The activity of Factor IX is obtained from the results of the Partial Thromboplastin Time (PTT).

The most reliable results are reached through quantitative assays on the activity of each of the Factors II, IX and X.

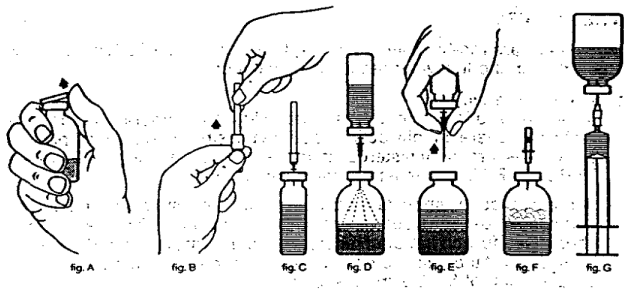
In acquired coagulation disorders which involve reduction of Factors II, VII, IX and X, the administration of vitamin K_1 is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K_1 in contrast to PROTHROMPLEX TIM 2 becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K_1 is no longer recommended because of occasional side-effects, it must be taken into consideration that by parenteral but not intravenous administration, a further delay in effectiveness will occur.

Reduction of the coagulation Factors VII and V, which may be involved in the above mentioned coagulation disorders, is not sufficiently influenced by PROTHROMPLEX TIM 2. ANTIHAEMOPHILIC PLASMA HUMAN "HAEMODERIVATE" (AHP) is recommended as a supplement.

RECONSTITUTION OF CONCENTRATE

PROTHROMPLEX TIM 2 is to be stored in lyophilised condition and should only be reconstituted immediately before administration. The solution must then be used promptly. Entered vials must not be reused.

1. Warm the unopened bottle containing 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 covers sealed by a weld mark. Break the weld (Fig. B) by twisting the covers. Remove the outer cover and insert the exposed needle into the rubber stopper of the solvent bottle (Fig. C).
4. Remove the inner cover 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). Solvent will be drawn into the concentrate bottle which is under vaccum.
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

1. 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.).
2. Disconnect the filter needle from the syringe and slowly (maximum rate of injection: 2 ml/min) inject the solution intravenously with the enclosed disposable intravenous needle (or the infusion set with a winged adapter).

If any other kit for reconstitution and administration than that enclosed is used, make sure that this kit contains an adequate filter.

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX TIM 2. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage.

In cases of inherited or congenital coagulation disorders high initial dosage is recommended in order to ensure a rapid and sufficient rise in the coagulation factors concerned and thus achieve a reliable cessation of bleeding. Here, as well as with the following maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of the factors (Factor II approx. 40 — 60 hours, Factor IX approx. 12 — 30 hours, Factor X approx. 20 — 60 hours) successful results are achieved by repeated administration of PROTHROMPLEX TIM 2 at intervals of 12—24 hours. To assure absolute control of treatment, the blood coagulation should be tested as far as possible with quantitative activity assays of each of the coagulation factors. Treatment should be rigidly maintained up to complete healing of the wounds, especially in cases of inherited coagulation disorders, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX TIM 2 lies in the fact that by application of small volumes of fluid and a slight amount of protein, a high concentration of coagulation factors (II, IX and X) is reached in the circulation. The danger of a volume or protein overloading of the patient is excluded even with the administration of higher doses.

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or splenoportography. They should previously receive sufficient PROTHROMPLEX TIM 2 to hold their Thromboplastin Time or Normotest value above 50% for several days.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), administration of PROTHROMPLEX TIM 2 should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

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1. Allergic Reactions
All forms of allergic reactions from mild and temporary urticarious rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once.
Allergic reactions should be controlled with antihistamines and glucocorticosteroids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. Despite the precautions taken in the selection of donors, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of glucocorticosteroids or immunosuppressive substances has hardly influenced the formation of inhibitors.

SHELF LIFE AND STORAGE

2 years when stored between +2° and -8°C

PACKS

Each containing the equivalent of 200 units or 500 units of Factor II, Factor IX and Factor X

1 R/C bottle containing lyophilized PROTHROMPLEX
1 R/C bottle containing 20 ml of Aqua ad Iniectabilia
1 kit for reconstitution and injection

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1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
2. FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6, 110:116 (1968)
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PROTHROMPLEX®

Partial Prothrombin Complex (Human)

II

Prothrombin Complex is understood to include the vitamin K, dependent coagulation Factors II, VII, IX and X.

PROTHROMPLEX contains coagulation Factors II, IX and X and is indicated for the treatment of all coagulation disorders due to lack of Factor II (Prothrombin), Factor IX (Christmas Factor), and Factor X (Stuart-Prower Factor).

MANUFACTURE AND COMPOSITION

PROTHROMPLEX is prepared from pooled plasma of healthy donors and freezedried for stability in storage. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for the absence of HB_s-antigen (RIA). Any donor who has a positive HB_s-antigen test, is permanently excluded from the donor programme. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out.

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor II as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit* of Factor II. Despite a moderate total protein content a high concentration of Factor IX and X is also reached. PROTHROMPLEX is distributed in packs containing either 500 or 200 units* of Factor II, IX and X.

INDICATIONS

Indications for PROTHROMPLEX include all types of haemorrhages caused by inherited or acquired coagulation disorders due to reduced Factor II, IX and/or X activity.

Treatment for inherited or congenital coagulation disorders

1. Hypo- or A-prothrombinaemia (Factor II deficiency)
2. Haemophilia B (Factor IX deficiency)
3. Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency)
4. Stuart-Prower Factor deficiency (Factor X deficiency)
5. Combined deficiency of Factors II, IX or X.

Treatment for acquired coagulation disorders

1. Haemorrhages due to a deficiency of Factors II, IX and X with severe damage of the liver parenchyma (hepatitis, cirrhosis of the liver, severe toxic liver damage through poisoning etc.).
2. Emergency treatment of severe acute haemorrhages which may occur during anticoagulant therapy. This is of especial use if anticoagulants are administered during the last three months of pregnancy. PROTHROMPLEX normalizes Factor II, IX and X activity.
3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROMPLEX, Factor II, IX and X activity is normalized.

* The activity in International Units (I.U.) Factor IX is expressed in terms of the relevant International Standard (WHO-Standard) for Blood Coagulation Factor IX Human.

Since the activity of the relevant International Standard is based on comparison with "average fresh normal plasma", 1 I.U. can also be defined as the *Factor IX activity present in* 1 ml average fresh normal plasma.

1 unit Factor II and X is equivalent to the activity of these Factors in 1 ml average fresh normal plasma.

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4. Severe acute haemorrhages caused by vitamin K deficiency (genuine vitamin K deficiency or as (for example) a consequence of resorption disturbances). Through the administration of PROTHROMPLEX Factor II, IX and X activity is normalized.

5. Before carrying out biopsies or pre-operative treatment of patients with Factor II, IX or X deficiencies.

By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor II, IX and X in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factors II and X is determined by the Thromboplastin Time (Quick value), the Thrombotest or Normotest. The activity of Factor IX is obtained from the results of the Partial Thromboplastin Time (PTT).

The most reliable results are reached through quantitative assays on the activity of each of the Factors II, IX and X.

In acquired coagulation disorders which involve reduction of Factors II, VII, IX and X, the administration of vitamin K_1 is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K_1 in contrast to PROTHROMPLEX becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K_1 is no longer recommended because of occasional side-effects, it must be taken into consideration that by parenteral but not intravenous administration, a further delay in effectiveness will occur.

Reduction of the coagulation Factors VII and V, which may be involved in the above mentioned coagulation disorders, is not sufficiently influenced by PROTHROMPLEX. ANTIHAEMOPHILIC PLASMA HUMAN "HAEMODERIVATE" (AHP) is recommended as a supplement.

ADMINISTRATION

PROTHROMPLEX 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 ml/min.

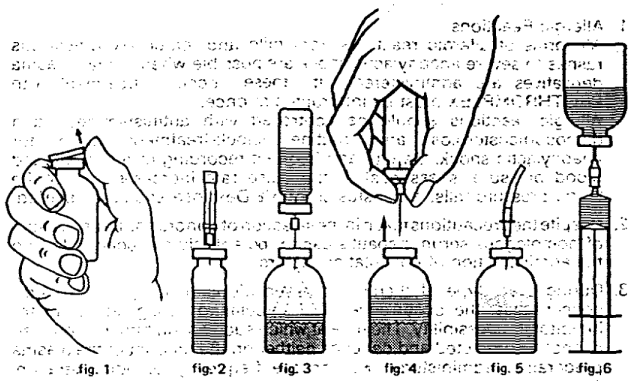

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

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

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage.

In cases of inherited or congenital coagulation disorders high initial dosage is recommended in order to ensure a rapid and sufficient rise in the coagulation factors concerned and thus achieve a reliable cessation of bleeding. Here, as well as with the following maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of the factors (Factor II approx. 40-60 hours, Factor IX approx. 12-30 hours, Factor X approx. 20-60 hours) successful results are achieved by repeated administration of PROTHROMPLEX at intervals of 12—24 hours. To assure absolute control of treatment, the blood coagulation should be tested as far as possible with quantitative activity assays of each of the coagulation factors. Treatment should be rigidly maintained up to complete healing of the wounds, especially in cases of inherited coagulation disorders, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein, a high concentration of coagulation factors (II, IX and X) is reached in the circulation. The danger of a volume or protein overloading of the patient is excluded even with the administration of higher doses.

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or splenoportography. They should previously receive sufficient PROTHROMPLEX to hold their Thromboplastin Time or Normotest value above 50% for several days.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), administration of PROTHROMPLEX should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX, though the following reactions may occur:

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PROTHROMPLEX®

Partial Prothrombin Complex (Human)

Prothrombin Complex is understood to include the vitamin K_1 dependent coagulation Factors II, VII, IX and X.

PROTHROMPLEX contains coagulation Factors II, IX and X and is indicated for the treatment of all coagulation disorders due to lack of Factor II (Prothrombin), Factor IX (Christmas Factor), and Factor X (Stuart-Prower Factor).

MANUFACTURE AND COMPOSITION

PROTHROMPLEX is prepared from pooled plasma of healthy donors and freezedried for stability in storage. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for the absence of HB_S-antigen (RIA). Any donor who has a positive HB_S-antigen test, is permanently excluded from the donor programme. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out.

Through appropriate purification and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor II as compared to fresh plasma. Thus 1 milligram of protein contains at least one unit* of Factor II. Despite a moderate total protein content a high concentration of Factor IX and X is also reached. PROTHROMPLEX is distributed in packs containing either 500 or 200 units* of Factor II, IX and X.

INDICATIONS

Indications for PROTHROMPLEX include all types of haemorrhages caused by inherited or acquired coagulation disorders due to reduced Factor II, IX and/or X activity.

Treatment for inherited or congenital coagulation disorders

1. Hypo- or A-prothrombinaemia (Factor II deficiency)
2. Haemophilia B (Factor IX deficiency)
3. Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency)
4. Stuart-Prower Factor deficiency (Factor X deficiency)
5. Combined deficiency of Factors II, IX or X.

Treatment for acquired coagulation disorders

1. Haemorrhages due to a deficiency of Factors II, IX and X with severe damage of the liver parenchyma (hepatitis, cirrhosis of the liver, severe toxic liver damage through poisoning etc.).
2. Emergency treatment of severe acute haemorrhages which may occur during anticoagulant therapy. This is of especial use if anticoagulants are administered during the last three months of pregnancy. PROTHROMPLEX normalizes Factor II, IX and X activity.
3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROMPLEX, Factor II, IX and X activity is normalized.

* The activity in International Units (I.U.) Factor IX is expressed in terms of the relevant International Standard (WHO-Standard) for Blood Coagulation Factor IX Human.

Since the activity of the relevant International Standard is based on comparison with "average fresh normal plasma", 1 I.U. can also be defined as the Factor IX activity present in 1 ml average fresh normal plasma.

* 1 unit Factor II and X is equivalent to the activity of these Factors in 1 ml average fresh normal plasma.

4. Severe acute haemorrhages caused by vitamin K deficiency (genuine vitamin K deficiency or as (for example) a consequence of resorption disturbances). Through the administration of PROTHROMPLEX, Factor II, IX and X activity is normalized.

5. Before carrying out biopsies or pre-operative treatment of patients with Factor II, IX or X deficiencies.

By administering an appropriate dose of PROTHROMPLEX, it is possible to achieve a prompt and sufficient rise of Factor II, IX and X in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factors II and X is determined by the Thromboplastin Time (Quick value), the Thrombotest or Normotest. The activity of Factor IX is obtained from the results of the Partial Thromboplastin Time (PTT).

The most reliable results are reached through quantitative assays on the activity of each of the Factors II, IX and X.

In acquired coagulation disorders which involve reduction of Factors II, VII, IX and X, the administration of vitamin K_1 is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K_1 in contrast to PROTHROMPLEX becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K_1 is no longer recommended because of occasional side-effects, it must be taken into consideration that by parenteral but not intravenous administration, a further delay in effectiveness will occur.

Reduction of the coagulation Factors VII and V, which may be involved in the above mentioned coagulation disorders, is not sufficiently influenced by PROTHROMPLEX. ANTIHAEMOPHILIC PLASMA HUMAN "HAEMODERIVATE" (AHP) is recommended as a supplement.

ADMINISTRATION

PROTHROMPLEX 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 ml/min.

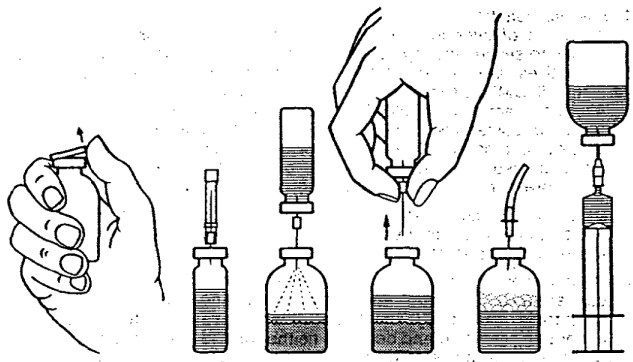

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

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

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

DOSAGE

Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage.

In cases of inherited or congenital coagulation disorders high initial dosage is recommended in order to ensure a rapid and sufficient rise in the coagulation factors concerned and thus achieve a reliable cessation of bleeding. Here, as well as with the following maintenance therapy, the initially short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of the factors (Factor II approx. 40-60 hours, Factor IX approx. 12-30 hours, Factor X approx. 20-60 hours) successful results are achieved by repeated administration of PROTHROMPLEX at intervals of 6-12 hours. To assure absolute control of treatment, the blood coagulation should be tested as far as possible with quantitative activity assays of each of the coagulation factors. Treatment should be rigidly maintained up to complete healing of the wounds, especially in cases of inherited coagulation disorders, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEX lies in the fact that by application of small volumes of fluid and a slight amount of protein, a high concentration of coagulation factors (II, IX and X) is reached in the circulation. The danger of a volume or protein overloading of the patient is excluded even with the administration of higher doses.

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or splenoportography. They should previosly receive sufficient PROTHROMPLEX to hold their Thromboplastin Time or Normotest value above 50% for several days.

PRECAUTIONS

With patients suffering from disseminated intravascular coagulation (DIC), administration of PROTHROMPLEX should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX though the following reactions may occur:

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1. Allergic Reactions
   All forms of allergic reactions from mild and temporary urticarious rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with PROTHROMPLEX must be interrupted at once.
   Allergic reactions should be controlled with antihistamines and glucocorticosteroids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls, a transfusion of 5% Dextrose should be started.
2. Despite the precautions taken in the selection of donors, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of administration. According to present experience the application of glucocorticosteroids or immunosuppressive substances has hardly influenced the formation of inhibitors.

SHELF LIFE AND STORAGE

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

PACKS

Each containing the equivalent of 200 units or 500 units of Factor II, Factor IX and Factor X

1 R/C bottle containing lyophilized PROTHROMPLEX
1 R/C bottle containing 20 ml of Aqua ad Iniectabilia
1 kit for reconstitution and injection

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

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BEBULIN© TIM 2

Factor IX Concentrate Human

Steam Treated

COMPOSITION AND PROPERTIES

BEBULIN TIM 2 contains the coagulation factor IX (Christmas Factor) in at least 50-fold concentration as compared to fresh plasma. 1 mg protein contains 0.85 to 2.5 I.U.[1] Factor IX.

To eliminate the potential risk of thrombogenic complications associated with Factor IX preparations BEBULIN TIM 2 is routinely tested for the absence of activated coagulation factors.

In addition, BEBULIN TIM 2 contains a small amount of heparin (max. 0.15 I.U.[2]) heparin per I.U. Factor IX).

When using BEBULIN TIM 2 in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboembolism is to be expected.

BEBULIN TIM 2 is prepared from pooled human plasma.

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 BEBULIN TIM 2 and the final product were tested for HB_S-antigen by Radio Immune Assay (RIA) and found non-reactive.
2. Steam Treatment Immuno Method 2
   BEBULIN TIM 2 is subjected to a model virus controlled product specific virusinactivation.

INDICATIONS

BEBULIN TIM 2 is indicated for treatment and prophylaxis of all coagulation defects caused by or associated with congenital or acquired Factor IX deficiency.

These are:

— Haemophilia B
— Congenital or acquired Factor IX deficiency with Factor IX inhibitor.
— Acquired Factor IX deficiency

CONTRAINDICATIONS

Suspected consumption coagulopathy:
administration of BEBULIN TIM 2 is recommended only after elimination of the underlying consumption disorder.

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 BEBULIN TIM 2.

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.

In the course of treatment with Factor IX preparations a circulating inhibitor directed against Factor IX may develop in rare cases.

Steam treatment reduces the risk of viral transmission in general and eliminates it specifically in some cases.

HTLV III for example, if added to a sample of the product is inactivated by a factor of 10^6.

However, despite the measures taken, the transmission of virus hepatitis cannot be ruled out.

INTERACTIONS

None known

DOSAGE AND ADMINISTRATION

Dosage

I. Haemophilia B

1. Spontaneous Bleeding

Individual dosage depends on the severity of the Factor IX defect, the localisation and the extent of the haemorrhage. The severity of haemophilia is judged by the residual Factor IX plasma concentration of the patient. Table 1 shows the Factor IX levels (in % of normal) required for the management of individual types of bleeding.

Localisation and extent of haemorrhage	Factor IX plasma level to be achieved by initial dose	Factor IX level during maintenance therapy	Duration of maintenance of indicated Factor IX level
Minor haemorrhage: e.g. Early stage of joint and muscle bleeding, epistaxis, bleeding into the oral cavity and minor trauma, haematuria	20%	20%	1—3 days
Major haemorrhage: e.g. Haemarthrosis or haematoma with pain and swelling, head trauma without neurological signs, severe trauma also without open bleeding, gastrointestinal bleeding, heavy abdominal pain, major injury	40%	20—40%	3—4 days or until adequate wound healing
Life threatening haemorrhage: e.g. Intracranial, intraabdominal or intrathoracic bleeding, severe injury, fractures	60%	40%	10—14 days or until adequate wound healing

Table 1: *Therapeutically required Factor IX plasma level (in % of normal)* for haemophilia B patients.

[1] 1 I.U. Factor IX (according to WHO standard) corresponds to the activity of Factor IX present in 1 ml of fresh average human plasma.
[2] 1 I.U. heparin according to WHO standard.

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To achieve the Factor IX plasma levels indicated in Table 1 dosage may be calculated according to the formula:

1 I.U. Factor IX/kg bodyweight – Factor IX plasma level increase of approx. 1%

This increase corresponds to an in vivo recovery of approx. 40%.

The residual Factor IX activity of the patient must be taken into consideration when calculating the dose.

Bodyweight kg	Plasma level increase % 20%	30%	40%	50%	60%
10	200	300	400	500	600
15	300	450	600	750	900
20	400	600	800	1000	1200
25	500	750	1000	1250	1500
30	600	900	1200	1500	1800
35	700	1050	1400	1750	2100
40	800	1200	1600	2000	2400
45	900	1350	1800	2250	2700
50	1000	1500	2000	2500	3000
55	1100	1650	2200	2750	3300
60	1200	1800	2400	3000	3600
65	1300	1950	2600	3250	3900
70	1400	2100	2800	3500	4200
75	1500	2250	3000	3750	4500
80	1600	2400	3200	4000	4800

Table 2: Loading doses for initial application in I.U. Factor IX based on a 1% increase in the Factor IX level after injection of 1 I.U. Factor IX/kg bodyweight.

The half life of Factor IX is 18 — 30 hours; thus, BEBULIN TIM 2 should be given at intervals of 12 — 24 hours depending on the individual bleeding situation.

In general, minor bleeding can be controlled by one half of the loading dose at 24 hour intervals. Major haemorrhage should be treated at 12 hour intervals with one half of the loading dose to prevent a decrease of the Factor IX plasma level below 20% towards the end of the substitution intervals.

Substitution therapy with BEBULIN TIM 2 must be continued until complete resorption of tissue haemorrhage or adequate wound healing.

2. Surgery

For elective surgery dosage calculations should allow for the fact that normally there is no increased consumption of Factor IX prior to surgical interventions, whereas during an operation and in the early postoperative hours the Factor IX consumption is considerably increased. Substitution treatment should be commenced 1 — 2 hours prior to the surgical intervention.

Surgery	Preoperative Factor IX level	Postoperative Factor IX level	
Minor surgery (e.g. dental extractions)	40%	40% 20—40%	Day of operation until adequate wound healing
Major surgery	60%	60% 40% 20%	Day of operation First week postoperatively From the second week postoperatively until adequate wound healing

Table 3: Therapeutically required Factor IX level (in % of normal) for surgical interventions.

According to clinical experience one half of the loading dose is required during the first postoperative days, and afterwards 1/4 of the loading dose administered at 12 hour intervals.

For monitoring the clinical course and calculating the precise dose required close laboratory control of the patient's Factor IX plasma level must be performed to prevent bleeding complications, delayed wound healing and serious sequelae.

3. Long Term Prophylactic Treatment

For long term prophylactic substitution in patients with severe haemophilia B a dose of 10 I.U./kg b.w. of BEBULIN TIM 2 should be administered twice a week.

II. Congenital or Acquired Factor IX Deficiency with Factor IX Inhibitor

In patients with a circulating inhibitor against Factor IX any substitution treatment with Factor IX concentrate should only be carried out to control severe bleeding. To obtain the required plasma concentration of Factor IX unusually high doses of BEBULIN TIM 2 may have to be administered, since part of the infused Factor IX is inactivated by the inhibitor (Attention: volume overload!).

Independent of the inhibitor titre the use of FEIBA IMMUNO (Anti Inhibitor Coagulant Complex with Factor Eight Inhibitor Bypassing Activity from IMMUNO AG, Austria) has proved both effective and safe in patients with Factor IX inhibitors.

Close laboratory control of the Factor IX plasma level to monitor the clinical course and to calculate the individually necessary dose is indispensable in the treatment of acquired or congenital Factor IX deficiency with Factor IX inhibitor.

III. Acquired Factor IX Deficiency

As to the required plasma level of Factor IX and maintenance of the therapeutic plasma level in patients with acquired Factor IX deficiency please see instructions for haemophilia B. However, depending on the cause of the Factor IX defect differing in vivo recoveries must be taken into consideration:

In patients under oral anticoagulants and in vivo recovery of 60 — 70% can be expected, in cases with acute hepatitis one of approx. 50%, while in patients with chronic liver damage the expected in vivo recovery is only 20 — 30%.

In case of vitamin K deficiency, apart from Factor IX also Factors II, VII, and X are decreased. BEBULIN TIM 2 contains Factors II and X, but not Factor VII. For simultaneous substitution of all four prothrombin complex factors treatment with PROTHROMPLEX TOTAL* (from IMMUNO AG, Austria) is recommended.

Additional Instructions

With dental extractions, trauma in the oral cavity and severe, prolonged epistaxis, local haemostatic control should be attempted in addition to replacement therapy with BEBULIN TIM 2.

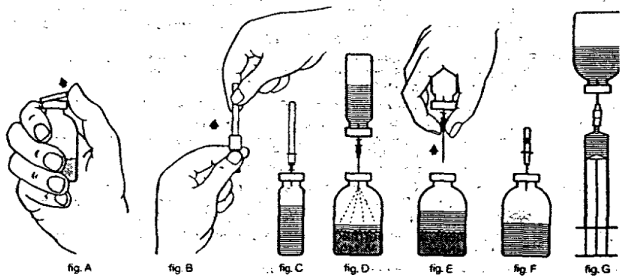
Antifibrinolytics (e.g. epsilon-aminocaproic acid) are also indicated in the above examples of local bleeding.

In exceptional cases of severe haemarthroses, aspiration may be necessary. Treatment with BEBULIN TIM 2 should then be started immediately following aspiration. BEBULIN TIM 2 must not be given before aspiration or a clot may form in the synovial cavity.

Reconstitution of Concentrate

BEBULIN TIM 2 is to be stored in lyophilized condition and should only be reconstituted immediately before application. The solution must then be used promptly. 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 (maximum rate of injection: 2 ml/min.) inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

If any other kit for reconstitution and application than that enclosed is used make sure that this kit contains an adequate filter.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +8°C or 6 months when stored at room temperature (up to 30°C).

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 30°C). Without cooling facilities BEBULIN TIM 2 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.

* A prothrombin complex preparation containing equal amounts of Factors II, VII, IX, and X.

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BEBULIN TIM 2 must not be used beyond the expiry date indicated.

Store out of the reach of children.

PACKS

BEBULIN TIM 2

— R/C vial containing 200 IU of lyophilized Factor IX
— R/C vial containing 10 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

— R/C vial containing 500 IU of lyophilized Factor IX
— R/C vial containing 10 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

— R/C vial containing 1000 IU of lyophilized Factor IX
— R/C vial containing 20 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

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

Store out of the reach of children.

PACKS

BEBULIN TIM 4

— R/C vial containing 200 IU of lyophilized Factor IX
— R/C vial containing 10 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

— R/C vial containing 500 IU of lyophilized Factor IX
— R/C vial containing 10 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

— R/C vial containing 1000 IU of lyophilized Factor IX
— R/C vial containing 20 ml Aqua ad Iniectabilia
— Kit for reconstitution and injection

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BEBULIN® TIM 4

Factor IX Concentrate Human

Steam Treated

COMPOSITION AND PROPERTIES

BEBULIN TIM 4 contains the coagulation factor IX (Christmas Factor) in at least 50-fold concentration as compared to fresh plasma. 1 mg protein contains 0.85 to 2.5 I.U.[1] Factor IX.

To eliminate the potential risk of thrombogenic complications associated with Factor IX preparations BEBULIN TIM 4 is routinely tested for the absence of activated coagulation factors.

In addition, BEBULIN TIM 4 contains a small amount of heparin (max. 0.15 I.U.[2]) heparin per I.U. Factor IX).

When using BEBULIN TIM 4 in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboembolism is to be expected.

BEBULIN TIM 4 is prepared from pooled human plasma.

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 BEBULIN TIM 4 and the final product were tested for HB_S-antigen by Radio Immune Assay (RIA) and found non-reactive.
2. Steam Treatment Immuno Method 4
   BEBULIN TIM 4 is subjected to a model virus controlled product specific virusinactivation.

INDICATIONS

BEBULIN TIM 4 is indicated for treatment and prophylaxis of all coagulation defects caused by or associated with congenital or acquired Factor IX deficiency.

These are:

— Haemophilia B
— Congenital or acquired Factor IX deficiency with Factor IX inhibitor.
— Acquired Factor IX deficiency

CONTRAINDICATIONS

Suspected consumption coagulopathy:
administration of BEBULIN TIM 4 is recommended only after elimination of the underlying consumption disorder.

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 BEBULIN 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.

In the course of treatment with Factor IX preparations a circulating inhibitor directed against Factor IX may develop in rare cases.

Steam treatment reduces the risk of viral transmission in general and eliminates it specifically in some cases.

HTLV III for example, if added to a sample of the product is inactivated by a factor of 10^6.

However, despite the measures taken, the transmission of virus hepatitis cannot be ruled out.

INTERACTIONS

None known

DOSAGE AND ADMINISTRATION

Dosage

I. Haemophilia B

1. Spontaneous Bleeding

Individual dosage depends on the severity of the Factor IX defect, the localisation and the extent of the haemorrhage. The severity of haemophilia is judged by the residual Factor IX plasma concentration of the patient. Table 1 shows the Factor IX levels (in % of normal) required for the management of individual types of bleeding.

Localisation and extent of haemorrhage	Factor IX plasma level to be achieved by initial dose	Factor IX level during maintenance therapy	Duration of maintenance of indicated Factor IX level
Minor haemorrhage: e.g. Early stage of joint and muscle bleeding, epistaxis, bleeding into the oral cavity and minor trauma, haematuria	20%	20%	1—3 days
Major haemorrhage: e.g. Haemarthrosis or haematoma with pain and swelling, head trauma without neurological signs, severe trauma also without open bleeding, gastrointestinal bleeding, heavy abdominal pain, major injury	40%	20—40%	3—4 days or until adequate wound healing
Life threatening haemorrhage: e.g. Intracranial, intraabdominal or intrathoracic bleeding, severe injury, fractures	60%	40%	10—14 days or until adequate wound healing

Table 1: Therapeutically required Factor IX plasma level (in % of normal) for haemophilia B patients.

[1] 1 I.U. Factor IX (according to WHO standard) corresponds to the activity of Factor IX present in 1 ml of fresh average human plasma.
[2] 1 I.U. heparin according to WHO standard.

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To achieve the Factor IX plasma levels indicated in Table 1 dosage may be calculated according to the formula:

1 I.U. Factor IX/kg bodyweight – Factor IX plasma level increase of approx. 1%

This increase corresponds to an in vivo recovery of approx. 40%.

The residual Factor IX activity of the patient must be taken into consideration when calculating the dose.

Bodyweight kg	Plasma level increase % 20%	30%	40%	50%	60%
10	200	300	400	500	600
15	300	450	600	750	900
20	400	600	800	1000	1200
25	500	750	1000	1250	1500
30	600	900	1200	1500	1800
35	700	1050	1400	1750	2100
40	800	1200	1600	2000	2400
45	900	1350	1800	2250	2700
50	1000	1500	2000	2500	3000
55	1100	1650	2200	2750	3300
60	1200	1800	2400	3000	3600
65	1300	1950	2600	3250	3900
70	1400	2100	2800	3500	4200
75	1500	2250	3000	3750	4500
80	1600	2400	3200	4000	4800

Table 2: Loading doses for initial application in I.U. Factor IX based on a 1% increase in the Factor IX level after injection of 1 I.U. Factor IX/kg bodyweight.

The half life of Factor IX is 18 — 30 hours; thus, BEBULIN TIM 4 should be given at intervals of 12 — 24 hours depending on the individual bleeding situation.

In general, minor bleeding can be controlled by one half of the loading dose at 24 hour intervals. Major haemorrhage should be treated at 12 hour intervals with one half of the loading dose to prevent a decrease of the Factor IX plasma level below 20% towards the end of the substitution intervals.

Substitution therapy with BEBULIN TIM 4 must be continued until complete resorption of tissue haemorrhage or adequate wound healing.

2. Surgery

For elective surgery dosage calculations should allow for the fact that normally there is no increased consumption of Factor IX prior to surgical interventions, whereas during an operation and in the early postoperative hours the Factor IX consumption is considerably increased. Substitution treatment should be commenced 1 — 2 hours prior to the surgical intervention.

Surgery	Preoperative Factor IX level	Postoperative Factor IX level	
Minor surgery (e.g. dental extractions)	40%	40% 20—40%	Day of operation until adequate wound healing
Major surgery	60%	60% 40% 20%	Day of operation First week postoperatively From the second week postoperatively until adequate wound healing

Table 3: Therapeutically required Factor IX level (in % of normal) for surgical interventions.

According to clinical experience one half of the loading dose is required during the first postoperative days, and afterwards 1/4 of the loading dose administered at 12 hour intervals.

For monitoring the clinical course and calculating the precise dose required close laboratory control of the patient's Factor IX plasma level must be performed to prevent bleeding complications, delayed wound healing and serious sequelae.

3. Long Term Prophylactic Treatment

For long term prophylactic substitution in patients with severe haemophilia B a dose of 10 I.U./kg b.w. of BEBULIN TIM 4 should be administered twice a week.

II. Congenital or Acquired Factor IX Deficiency with Factor IX Inhibitor

In patients with a circulating inhibitor against Factor IX any substitution treatment with Factor IX concentrate should only be carried out to control severe bleeding. To obtain the required plasma concentration of Factor IX unusually high doses of BEBULIN TIM 4 may have to be administered, since part of the infused Factor IX is inactivated by the inhibitor (Attention: volume overload!).

Independent of the inhibitor titre the use of FEIBA IMMUNO (Anti Inhibitor Coagulant Complex with Factor Eight Inhibitor Bypassing Activity from IMMUNO AG, Austria) has proved both effective and safe in patients with Factor IX inhibitors.

Close laboratory control of the Factor IX plasma level to monitor the clinical course and to calculate the individually necessary dose is indispensable in the treatment of acquired or congenital Factor IX deficiency with Factor IX inhibitor.

III. Acquired Factor IX Deficiency

As to the required plasma level of Factor IX and maintenance of the therapeutic plasma level in patients with acquired Factor IX deficiency please see instructions for haemophilia B. However, depending on the cause of the Factor IX defect differing in vivo recoveries must be taken into consideration:

In patients under oral anticoagulants and in vivo recovery of 60 — 70% can be expected, in cases with acute hepatitis one of approx. 50%, while in patients with chronic liver damage the expected in vivo recovery is only 20 — 30%.

In case of vitamin K deficiency, apart from Factor IX also Factors II, VII, and X are decreased. BEBULIN TIM 4 contains Factors II and X, but not Factor VII. For simultaneous substitution of all four prothrombin complex factors treatment with PROTHROMPLEX TOTAL* (from IMMUNO AG, Austria) is recommended.

Additional Instructions

With dental extractions, trauma in the oral cavity and severe, prolonged epistaxis, local haemostatic control should be attempted in addition to replacement therapy with BEBULIN TIM 4.

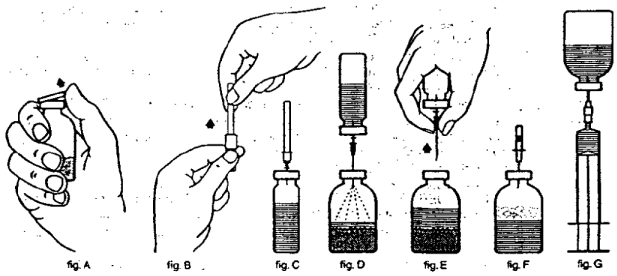
Antifibrinolytics (e.g. epsilon-aminocaproic acid) are also indicated in the above examples of local bleeding.

In exceptional cases of severe haemarthroses, aspiration may be necessary. Treatment with BEBULIN TIM 4 should then be started immediately following aspiration. BEBULIN TIM 4 must not be given before aspiration or a clot may form in the synovial cavity.

Reconstitution of Concentrate

BEBULIN TIM 4 is to be stored in lyophilized condition and should only be reconstituted immediately before application. The solution must then be used promptly. 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 (maximum rate of injection: 2 ml/min.) inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

If any other kit for reconstitution and application than that enclosed is used, make sure that this kit contains an adequate filter.

SHELF LIFE AND STORAGE

2 years when stored between +2° and +8°C or 6 months when stored at room temperature (up to 30°C).

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 30°C). Without cooling facilities BEBULIN 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.

* A prothrombin complex preparation containing equal amounts of Factors II, VII, IX, and X.

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