GENEHMIGUNG DES LÄNDERSPEZIFISCHEN* LABELING

o BEIPACKTEXT

o ETIKETTIERUNG

für Produkt PROTHROMPLEX^{R} TIM 4

Land ENGLAND

Nr. Datum

Ländersachbearbeiter Registrierungsabt. _____ am _____

Abteilungsleiter Registrierungsabt. _____ am _____

Übersetzer _____ am _____

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

Klinische Forschung ** _____ am _____

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

zuständiger Konzessionär _____ am _____

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

** bei sachlichen Änderungen, bei USA in jedem Fall

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

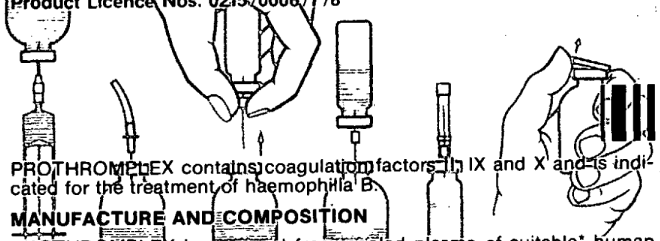
Prothromplex® TIM 4

P.O.M.

Partial Prothrombin Complex (Human)

heat-treated

Product Licence Nos. 0215/0006/7/8



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.

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 HBs-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.

* 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

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

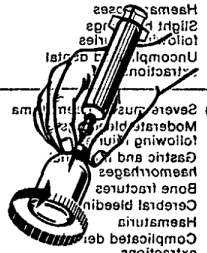
The lyophilised PROTHROMPLEX must be dissolved immediately before injection using the amount of solvent provided (10 ml).

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.

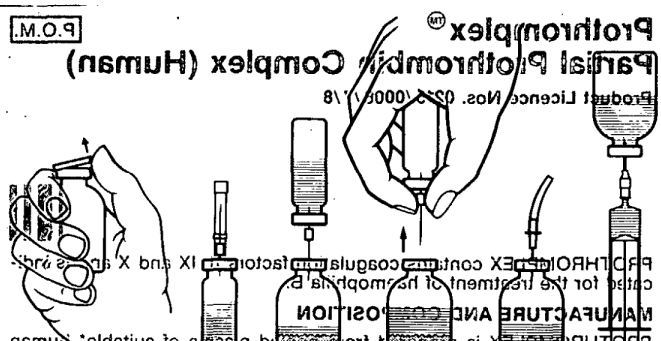
B) a) Transfer of the solvent into the bottle containing the lyophilisate is done with the help of the transfer needle. For this purpose first remove the protective cap of the transfer needle and insert the latter into the rubber stopper of the bottle containing the solvent (fig. 2).

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).



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

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

The most reliable results are obtained by quantitative assay in vitro.

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

One unit of Factor IX/kg body weight = 1% increase in 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 Haematuria Slight bleedings following injuries Uncomplicated dental extractions	15-30 %	20-30 U	15-30 U
B) Severe muscle haematoma Moderate bleedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleedings Haematuria Complicated dental extractions	30-50 %	40-60 U	20-30 U
C) Major surgery	more than 50%	75 U	50 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. 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.

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

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INNER LABEL

PROTHROMPLEX^{R} TIM 4 200

Partial Prothrombin Complex Human heat-treated

Contains 200 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0006

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.

Agitate gently during reconstitution to avoid frothing.

The solution must be injected intravenously immediately after reconstitution

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

For reconstitution observe the directions given in the circular enclosed.

The reconstituted preparation contains 0.8-1.2 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
$Citrate^{3-}$	41 mEq/litre

Contains no preservative

Store between 2° and 6°C, protected from light.

P.O.M.

Batch No.:

Exp. Date:

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PROTHROMPLEX^{R} TIM 4 200

Partial Prothrombin
Complex Human
heat-treated

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Partial Prothrombin
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Partial Prothrombin
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Contains 200 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised
Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

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Store between 2° and 6°C, protected from light.

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Agitate gently during reconstitution to avoid frothing.

The solution must be injected intravenously immediately after reconstitution.

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PROTHROMPLEX^{R} TIM 4 200

Partial Prothrombin
Complex Human
heat-treated

CARTON

The reconstituted preparation contains 0.8–1.2 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^{+}	178 mEq/litre
Cl^{-}	137 mEq/litre
Citrate^{3-}	41 mEq/litre

For reconstitution observe the directions given in the circular enclosed.

Contains no preservative

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OUTER CARTON

PROTHROMPLEX^{R} TIM 4 200

Partial Prothrombin Complex
Human
heat-treated

Contains 200 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

PROTHROMPLEX^{R} TIM 4 200

Partial Prothrombin Complex
Human
heat-treated

Contains 200 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0006

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.
Agitate gently during reconstitution to avoid frothing.

For reconstitution observe the directions given in the circular enclosed

Enclosed: 10 ml of Water for Injections B.P.
Kit for reconstitution and injection

The solution must be injected intravenously immediately after reconstitution.

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

The reconstituted preparation contains 0.8-1.2 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
Citrate^{3-}	41 mEq/litre

Contains no preservative P.O.M.

Store between 2° and 6°C, protected from light.

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

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INNER LABEL

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin Complex Human

heat-treated

Contains 500 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0007

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.

Agitate gently during reconstitution to avoid frothing.

The solution must be injected intravenously immediately after reconstitution

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

For reconstitution observe the directions given in the circular enclosed.

The reconstituted preparation contains 2-3 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
$Citrate^{3-}$	41 mEq/litre

Contains no preservative

Store between 2° and 6°C, protected from light.

P.O.M.

Batch No.:

Exp. Date:

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PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin
Complex Human
heat-treated

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin
Complex Human
heat-treated

Contains 500 units* ($\pm$ 25%)
of each, Prothrombin (Factor II),
Christmas Factor (IX), and
Stuart-Prower Factor (X)

Lyophilised
Prepared from a plasma pool
of 1000 HB_s-Ag negative
donors.

To be reconstituted with 10 ml of Water for Injections B.P.

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

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Product Licence
no. 0215/0007

Batch No.:

Exp. Date:

P.O.M.

Store between 2° and 6°C,
protected from light.

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Telephone: Sevenoaks (0732)
458101

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin
Complex Human
heat-treated

Contains 500 units* ($\pm$ 25%)
of each, Prothrombin (Factor II),
Christmas Factor (IX), and
Stuart-Prower Factor (X)

Agitate gently during
reconstitution to avoid
frothing.

The solution must be injected
intravenously immediately after
reconstitution.

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

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin
Complex Human
heat-treated

CARTON

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin
Complex Human
heat-treated

The reconstituted preparation contains 2-3 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^{+}	178 mEq/litre
Cl^{-}	137 mEq/litre
Citrate^{3-}	41 mEq/litre

For reconstitution observe the directions given in the circular enclosed.

Contains no preservative

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OUTER CARTON

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin Complex
Human
heat-treated

Contains 500 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0007

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.
Agitate gently during reconstitution to avoid frothing.

For reconstitution observe the directions given in the circular enclosed

Enclosed: 10 ml of Water for Injections B.P.
Kit for reconstitution and injection

The solution must be injected intravenously immediately after reconstitution.

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

PROTHROMPLEX^{R} TIM 4 500

Partial Prothrombin Complex
Human
heat-treated

Contains 500 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

The reconstituted preparation contains 2-3 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
$Citrate^{3-}$	41 mEq/litre

Contains no preservative P.O.M.

Store between 2° and 6°C, protected from light.

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

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INNER LABEL

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex Human heat-treated

Contains 1000units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0008

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.

Agitate gently during reconstitution to avoid frothing.

The solution must be injected intravenously immediately after reconstitution

* One 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 1st International Standard for Blood Coagulation Factor IX, Human, 72/32.

For reconstitution observe the directions given in the circular enclosed.

The reconstituted preparation contains 4-6 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
$Citrate^{3-}$	41 mEq/litre

Contains no preservative

Store between 2° and 6°C, protected from light.

P.O.M.

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PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin
Complex Human
heat-treated

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex Human heat-treated

Contains 1000 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised
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PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex Human heat-treated

Product Licence no. 0215/0008

Batch No.:

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Store between 2° and 6°C, protected from light.

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PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex Human heat-treated

Contains 1000 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Agitate gently during reconstitution to avoid frothing.

The solution must be injected intravenously immediately after reconstitution.

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

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin
Complex Human
heat-treated

CARTON

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex Human heat-treated

The reconstituted preparation contains 4-6 per cent. w/v of total protein and 0.1 i.u. of Heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^{+}	178 mEq/litre
Cl^{-}	137 mEq/litre
Citrate^{3-}	41 mEq/litre

For reconstitution observe the directions given in the circular enclosed.

Contains no preservative

Production Division of
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OUTER CARTON

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex
Human
heat-treated

Contains 1000 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

PROTHROMPLEX^{R} TIM 4 1000

Partial Prothrombin Complex
Human
heat-treated

Contains 1000 units* ($\pm$ 25%) of each, Prothrombin (Factor II), Christmas Factor (IX), and Stuart-Prower Factor (X)

Lyophilised Product Licence no. 0215/0008

Prepared from a plasma pool of 1000 HB_s-Ag negative donors.

To be reconstituted with 10 ml of Water for Injections B.P.
Agitate gently during reconstitution to avoid frothing.

For reconstitution observe the directions given in the circular enclosed

Enclosed: 10 ml of Water for Injections B.P.
Kit for reconstitution and injection

The solution must be injected intravenously immediately after reconstitution.

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The reconstituted preparation contains 4-6 per cent. w/v of total protein and 0.1 i.u. of heparin per unit of Factor II.

Approx. electrolyte concentration:

Na^+	178 mEq/litre
Cl^-	137 mEq/litre
$Citrate^{3-}$	41 mEq/litre

Contains no preservative P.O.M.

Store between 2° and 6°C, protected from light.

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

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