

IMMUNO

Aktiengesellschaft für chemisch-medizinische Produkte

IMMUNO LTD. Att. Mr. Coombes

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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.

Produktionsbetrieb: Österreichisches Institut für Haemoderivate Ges.m.b.H.

01100101000/523

UK Specific Texts

PROTHROMPLEX

PROTHROMPLEX, untreated

110979

6205911EA01			VΑ	16.01.1986
6205911EA02	FG	20.07.1984	VA	10.07.1986

PROTHROMPLEX TIM 4, Heat Treated

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

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	V۵	14.07	1986
02032125401	T. G	27.02.1702	10		

PROTHROMPLEX TIM 2, Steam Treated

6205212EW51	MWG	7.02.1986	VA	2.07.1987
	FG	27.03.1986		
2				

PROTHROMPLEX TIM 4, Steam Treated

6205212EW02	MWG FG	6.02.1986 7.04.1986	VA	1.08.1989
6205212EW03	MWG FG	27.01.1987 10.06.1987	cur	rently 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	12.07.198	5
	FG	10.10.198	5

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

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.

- 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.
- The risk of transmission of viral hepatitis is most probably eliminated by 3 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 PRO-THROMPLEX 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

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 SOULER J.P.: STEINBUCH M.: Über die Herstellung und klinische Anwendung von Gerinnungs-taktoren- Konzentraten aus menschlichem Plasma. Z. Ges. Med. 20: 311 (1965)
 TULUSJ., BREEN F.A.: Christmas Factor Concentrates. The Clinical Use of Several Preparations. Bibl. haemat. No. 34: pp. 40 51 (1970)

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Manufactured by OSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H. Production Division of

IMMUNO AG Vienna Austria 6205911EA10/5-2

62 D5 9M EA 10

Prothromplex® P. O. M Partial Prothrombin Complex Human, **Steam Treated** (Method S-2)

PROTHROMPLEX contains coagulation factors II, IX and X and it 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 contains at least one concentration of Factor II and X is also reached. The second state

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 heparir (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** humar 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 o HB_s-antigen; the plasma pool is also tested for the absence of HTLV-II 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 x 10⁶/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.

- 1... Warm the unopened bottle containing the solvent to room temperature (max. 37°C).
- 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).
- 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 undervacuum. - for the solvent will be drawn into the concentrate bottle which is undervacuum. - for the solvent will be the solven
- 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

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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) 3^{-3} , 3^{-

Disconnect the fitter 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.

(c) BROWER BOARD (C) LOOP (FOR CONTRACT OF CONTRACT) (C) CONTRACT, CONTRA

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: (Crother and Severe Severe Construction of the s

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			erenî Li terenî
Haemarthroses	510%	15 U	7—15 U
Slight bleeding following injuries Upcomplicated dental		ر می افران ا	Methods (1)
extractions	Star Same	A CARACTER ST	192
 B) Severe muscle haematoma Moderate bleeding 	1 1.		
following injuries Gastric and intestinal basmorrhades		1.1.6.2.	
Bone fractures	1530%	. 20—30 U	15—30 U ~ .
Gerebrat bleeding Haamaturia			E.1.5
Complicated dental extractions Minor surgery	15: 11 1:5: 11	en els en Second	1 ng 2
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 completely 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

Most nove the protective case is the MIT '® xelqmonthrough Partial Prothrombin Complex (Human) ht 2 dec syrictio ા કરવાના આવેલી જોકાર કે ગોધવાલી અને ગોધવાલી ગોધવાલી heat-treated

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GMEX-06

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

MANUFACTURE AND COMPOSITION and principle dicional (b

MANUFACTURE AND COMPOSITION and the set of t

obulius etc. al

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 HBsantigen by Radio Immune Assay.(RIA) and found non-reactive.

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

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. Factor IX. Ę 言のと

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.

* S - SU981

Suitable human donors as described in the British Pharmacopoela Addendum 1978 under Dried Antihaemophilic Fraction. This is the nucleon state of the Addendum 1978 under

1 i.u. heparin according to WHO standard. .beev a upitutile.toos 2. Bemove the protective caps (fig. 1) and disinfect the rubber stoppers of

A a) Fit a disposable needle onto a syringe of suitable size. 3. Insert the needle of the syringe into the R /C bottle with solvent b) and draw up the solvent into the sytinge; 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 C C DE A en proves. the bottle draws in the solvent. d) Carefully dissolve the lyophilisate by gentle agitation (approx. 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). 11.0789 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 user the latter into the rubber stopper of the lyophilisate bottle user 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. Insert the provided aeration needle and any foam will collapse C) (fig. 5). Remove the aeration needle. d) Fit the enclosed filter needle onto the disposable syringe and - 21 . draw up the solution into the syringe (fig. 6). sterros pr in a service a service of the servic



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

DE EFFECTS

Only general directions can be given for the dosage of PROTHROMPEE TIM 4. It is dependent upon the seventy of the coagulation detect and the degree of the traumatic and haemorrhagic tissue damage. The suggeste dosage for the treatment of Haemophilia Brisigiven in the dosage gut below the treatment of Haemophilia Brisigiven in the dosage gut below the treatment of Haemophilia Brisigiven in the dosage gut gut? ZBLSWCSHT0201 is write material busise exect the presentations Dosage_guideofor/the treatment_of_severecandosemi-severe cases (Haemophilla B: Newly theme on Hours endlor book evaluated and driv 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 and considered account to equivariant of the patient's plasma and considered account of the patient's and a second account of the plasma account of the

Clinical Manifestation is on in consistent to consolve on constant di se evistencia consolve on consolve entre entre entre vocase consolve of manifestation entre entre entre vocase consolve of manifestation entre entre entre entre entre entre entre entre ent	Therapeutically wanted Minimum Factor IX level	Thitial dose in the units Factor, IX no. per kg, body and weight weight	Maintenanice dosu at intervals of; 6 to 12 (24) hrs. in units Factor IX per kg. body weight
A) Surface bleedings of the skin and mucosae	an in subset o Agina subset an	neth i ceitean Neth ibr viett	en nussu no ente let
Superficial or deep haematoma		2HOITA:	ONTRAINOR
Haemarthroses Stocker R.		1999 J5 UCIDE.	-210 -7
Slight bleedings	·安林县 - 12111	ur Malischibos	pubrua isrativ
Tollowing injuries.	PM018 1, 19934	C anoatais c	inise-crenent en
extractions	bae in esta	I negalized i	b noitestainima
1	1. 1. 2. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	<u>xa :::•#0:2147.1</u>	<u> </u>
B) Severe muscle haematoma	in a an saor na	ভাৰই নেগ লোক	soitse: « goive
Moderate bleedings	1		a ent méluped
Gastric and intestinal		BEAROTS 6	NA BREE¶UBH
Bone fractures	15-30%	20	15-30 U
Cerebral bleedings			5500
Haematuria			
Complicated dental	la presidente de	ਹੇ ਅਤੇ ਇੱਕ ਦਿੱਤਾ ਹੈ।	n sa sanah ka ta
Minor surgery	perior en ces secondo en ces	henedyi ger oor. Marriat oorigiere	as entrop on R on effection G
C) Major surgery	more than 50%	ojni or 75 (104 m	50-75 U

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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 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 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 uantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds hav heated completely, thus ensuring a complication-free postoperative course. The special advantage of PROTHROMPLEXTIM 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 date of the protein curve of the protein to envided one The danger of volume or protein overloading of the patient is avoided even with the administration of high doses. OT 3 Or CRMM with the administration of high doses. UT3 OF CAMP General Control Con

PRECAUTIONS Construction of the coagulation actors has been previously interrupted of the coagulation actors has been previously int THE A AMEN' DA ONUMM with Heparin. 🔅

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SIDE EFFECTS

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Side effects are rarely observed during treatment with PROTHROMPLEX TIMed though the following reactions, may occur; the company of the thir hetAllergic Reactions to subset of the ministered are blic much of the sector ob All forms of allergic reactions from mild and temporary unicarial rashes to severe anaphylactic shock are possible when human derivatives are administered. If these occur, treatment with PROTHROMPLEX TIM 4 built the sector of th

- to must be interrupted at occur, treatment with FNO Inhotop EcA third 4 to must be interrupted at once: Allergio: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 anti-body is a possibility. The time at which such an antibody is produced or anot, be predicted and depends neither on the amount of the plas-ma 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. Despite the measures taken to reduce the risk, the transmission of viral
- 3. 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-lifesaving situations in liver disease patients and those undergoing anticoagulant therapy.

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SHELF LIFE AND STORAGE

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

PACKS

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of 200 units; 500 units; or 1000 units of Factor II, IX and X in each container. 1 B/C bottle containing lyophilized PROTHROMPLEX TIM 4 1 B/C bottle containing 10 ml Water for Injections, B.P. 1 Kit for reconstitution and injection.

REFERENCES

REFERENCES BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Biackwell, Oxford (1966) 2: FISCHER M.: Die Blutererkrankung. Wien. med. Wschr. 6; 110:116 (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 Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. C. There, Stuttgart (1971) 5: LANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. C. Theme, Stuttgart (1971) 5: LANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBERGK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. C. MANDBECK G.: Störungen der Hämostaste. In Lawin P.: Praxis 'der Intensivbehandlung. G. MANDBERGK G.: Störungen der Hämostaste. Interator in Hämophilia B.: Thrombos. Diathes: D.: Hämmer Hämen Hämber A.: Störungen der Hämen Störung. B.: Störungen der Hämstänsen Störungen der Hämen Störung. J. B. J. BREEN IF.A.: Christiams: Factor: Concentrates. The Chinical Use of Several Preparations. Bibl. haemat. No. 34, pp. 40:51 (1970) Rott Hause, Preparations. Bibl. haemat. No. 34, pp. 40:51 (1970) Arctic House, Rye Lane, Dunton Green, Nr. Couroncate, Kont Ni 14 5HB

Arctic House, Rye Lane, Dunton Green, Nr. Sevenoaks, Kent TN 14 5HB Tel.: Sevenoaks (0732) 458101 Manufactured by OSTERREICHISCHES INSTITUT.

FUR HAEMODERIVATE GES.M.B.H. Production Division of the state of the IMMUNO AG Vienna Austria 6205911EA06/133ef



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Prothromplex® TIM 4 and approximately and an according Partial Prothrombin Complex (Human) in heat-treated 劉福 and drew up the solvent into

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FIGURE STREWEIGE REPORT PROTHROMPLEX TIM & contains coagulation factors II, IX and X and is PROTHEOMPUES TIME contains countering the protection of hat a protection of hat a protection of the solution o

MANUFACTURE AND COMPOSITION Set & HORD C VIULEDED

MANUFACTURE AND COMPOSITION of the react vibrate to be PROTHROMPLEX TIM 4 is prepared from pooled plasma of suitable' human donors and freeze oried 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 as properties a moderale total protein contains at least one unit. 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. So the absence of activated coagulation factors is subjected in addition, PROTHROMPLEX TIM 4 in the recommended dosage no activation of coagulation which may precipitate consumption coagulopathy or thromboemolism is to be expected. The dosage is an addition of coagulation which may precipitate consumption coagulopathy or thromboemolism is to be expected. To decrease the potential risk of throms is on the absence of coagulation which may precipitate consumption coagulopathy or thromboemolism is to be expected. The dosage is a subject of the other is and other what is a botten of coagulation which may precipitate consumption coagulopathy or thromboemolism is to be expected. The dosage is a subject of the other is an other what in the following steps are taken. The following is an other what indications and pools of plasma used, in the manufacture of

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. 50 2.

Thermoinactivation by Method TIM 4: PROTHROMPLEX TIM 4, is subjected to a model virus controlled

INDICATIONS

1

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.

plasma. Theieffectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thomboplastin Time (PTT). The most reliable results are obtained by quantitative activity assays of: Factor IX. Q

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. second to anothe the device the the needs are it up and

Dos units en una described in the British Bush of the Adendum 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 tresh hormat plasme. The Factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat plasme. The Factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat plasme. The Factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat plasme. The Factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat plasme. The factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat plasme. The factor IX Antis are expressed in terms of the set in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX activity present in 1 ml of average tresh hormat are to the factor IX and X activity present in 1 ml of average tresh hormat are to the factor IX antis activity present in 1 ml of average tresh hormat are to the factor IX antis activity present in 1 ml of average tresh hormat are to the factor IX antis activity present are to the factor IX antis activity present are to the factor IX activity present are to the factor IX antis activity present are to the factor IX antis activity present are to the factor IX activity present are to the factor IX activity present are to the factor IX activity presen

1 i.u. heparin according to WHO standard. reconstituiren is used.

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2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles 3

- 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 3000 arcc and draw up the solvent into the syringe; remove the needle from the syringe. Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the QC bette containing
- 1.03 X
 - into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.

Carefully dissolve the lyophilisate by gentle agitation (approx. d)

- 2-3 min.).
 e) Insert the provided aeration needle and any foam will collapse.
 e) Remove the aeration needle and draw up the solution into the solution in 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).
- an io 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 bobbilistic bottle bottle of the stopper 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).



- Separate the syringe from the filter needle and fit the enclosed 4. 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

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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 Bisigiven in the dosage guide below: control subtract of the education are control bits (control and estimate of Control and Child and a method subtraction by the best control of Control and Child and a method subtraction by the best control and the best control

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. proved converse 1.653.00

<mark>itient's plasma.</mark> So det om soll oversen og soll en en et alle om helter var en soll overse oversen om et alle en et alle oversen oversen soll en et alle et alle

Clinical Manifestation of Marian Maria and Antonio Maria Maria and Antonio Maria Maria and Antonio Maria	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX per kg. body weight	Maintenance dose at intervals of a 6 to 12 (24) hrs. in units Factor IX per kg. body weight.
A) Surface bleedings of the	1951 - 1970 1951 - 105 FM	na 2000 an Alber Na 1911 An Andre	ার ও প্রথমন ১.২৮ প্রের্ডার্ডার
Skin and mucosae Superficial or deep haematoma		8년21년~	9196 AS 5201
Haemarthroses	5		: 715 U (1981
Slight bleedings	- 16 Putto	na e tra	ುನ್ನ ಎಡ್.ೆ
Uncomplicated dental		14 Set 20	94 C - St. 9
extractions			an an shi sangingi (b
B) Severe muscle haematoma Moderate bleedings	و دره د م	Service Sector	, oscarna galari Nari grada nari
following injuries Gastric and intestinal		Presiditti -	a viu šina
Bone fractures	15-30%	2030 U	15—30 U
Cerebral bleedings			- 400
Haematuria	· · ·	· · · ·	and a straight of the straight
extractions			
Minor surgery	na an an ann an Anna Anna Anna Anna Anna		
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 PRO-THROMPLEX 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 resoration of the tissue haemorrhage or unit the wounds have 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. CASH

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.

6.00

SIDE EFFECTS

DOSAGE

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BAUGADO

Side, effects are rarely observed, during, treatment with PROTHROMPLEX, TIM 4, though the following reactions may accurate inspirated as a second to Allergic Beactions as a second by participation of the clismical additional generation of the second

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

to must be interrupted at once Allergio 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 of the pulse rate increases and for the blood pressure falls, a XI transfusion of 5% Destrose should be started XI (2007)

During every type of therapy involving blood or coagulation factor-concentrates, the occurrence of a circulating coagulation factor anti-body is a possibility. The time at which such an antibody is produced.

cannot be predicted and depends neither on the amount of the plas-ma 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.

Despite the measures taken to reduce the risk, the transmission of viral 3. hepatitis or other viral infections cannot be ruled outcome-

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-lifesaving situations in liver disease patients and those undergoing anticoagulant therapy. 220-22

SHELF LIFE AND STORAGE

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

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

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REFERENCES
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IMMUNO AG Vienna Austria 6205911EA04/133ef



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

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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 Used for the production and the absence of HBs antigen. Any donor who has a history of a pathological transaminase level or a positive HBs antigen test, is permanently excluded from the donor programme. Each batter of the final product is fested for absence of HBs antigen as well as to discount the level or a positive HBs antigent test, is permanently excluded from the donor programme. Each batter of the final product is fested for absence of HBs antigen as well as to discount the level of a positive HBs of the second se can only be tessened and not completely ruled but and beaus ton co Through, appropriate, purification, and concentration of the coagulation factors, one obtains at least a 60-fold concentration of Factor. [X 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

DOSAGE

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UDICATIONS UP attended to the second 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) 2000 to instruct oct and ables The most reliable results are obtained by quantitative activity assays of Factor, IX, other the state of several and the state of t

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.

Choose one of the two following procedures. 3

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

- 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.
- Fit the enclosed filter needle c) 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 Liq = 2 bus done with the help of the transfer needle. For this purpose to 6 of the transfer needle and insert vgstudt after into the rubber stopper of the bottle-containing the solvent be solved (fig. 2) son stress and happone to be the test forde villet a containing the solvest of the solvest o

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inference (southinsterbottler (fig., 4): Gently agitate the latter in order to renorm of accelerate solution actor in order to reiter neutranosoo spirit p

betarws cy Insert the provided aeration needle and any toam will collapse (fig. 5). Remove the aeration needle area of the set

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

48017040389 Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Praction 3 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 rili

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DOSAGE

Contracticités Only general directions can be given for the dosage of PROTHROMPLEX. It is dependent upon the severity of the coagulation detect and the degree of the traumatic and haemorrhagic fissue damage. The suggested dosage for the traumatic and haemorphilia B is given in the dosage guide below. Desage guide for the treatment of several and several several and several and several and several and several and several sever Bosage guide for the treatment of severe and semi-severe cases of Haemophilia Bta overationary and the series of a case of a c Formula for the calculation of the necessary quantity of Factor 1X¹¹⁷⁸ One unit of Factor IX/kg body weight = 1% increases of sactor 1X in the patient's plasma and noticed safe to noticulate as Birth chadge iG

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Clinical Manifestation	Therapeutically wanted Minimum Factor IX level	Initial dose in units Factor IX361 per kg. body weight. 2010	Maintenance dose at intervals of st 6 to 12 (24) hrs. in units Factor IX per kg. body, weight
A) Surface bleedings of the 200 skin and mucosae	a servici de la	nariawa na la	and we again the state
Superficial or deep. C	ીંગ્દ્ર વેલ્ડ મો	ສະຄຸດພະກວຽມປະ	115 A.
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B) Severe nusce haematoma		tat i ke shi je je	1.1
Moderate bleedings		a aprilave stati	ertap. An A
Gastric and intestinal haemorrhages	0 i 57.	intro 295 a m	+ ,55
Bone fractures	15-30%	20-30 U	15-30 U
Cerebral bleedings	6. 7.0.2	1 UG - 9801 /	Carlos de
Complicated dental	EN CO	· · · · · · · · · · · · · · · · · · ·	
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The danger of volume or protein overloading of the patient is avoided even with the administration of high doses in $e_{\rm convert}$ (c. p.i)

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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 Honarin

SIDE EFFECTS

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

Alleroic 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.
- Despite the precautions taken, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
- During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor anti-body is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plas-ma 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)
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Production Division of IMMUNO AG Vienna Austria

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Prothromplex[®] Partial Prothrombin Complex (Human) 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. All donors whose plasma is used for the production of PROTHROMPLEX are tested at each donation for their GPT level and the absence of HBs-antigen. Any donor who has a history of a pathological transaminase level or a positive HBs-antigen test, is permanently excluded from the donor programme. Each batch of the final product is tested for absence of HBs-antigen as well as to discount the likelihood of provoking disseminated intravascilar coagulation. Despite these precautions, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled jout. The brocks to not 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 contains at least one contration 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.
- 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 deration 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 Pharmacoppers 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 clasma. The Factor IX units are excressed in terms of the 1st International Standard for Blood Coagulation Factor IX. Human 72, 32



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 Superticial or deep haematoma Haemarthroses Slight bleedings following injuries Uncomplicated dental extractions	5-10%	- 15 U	7-15 U
B) Severe muscle haematoma Moderate bieedings following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bieedings 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 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 PRO-THROMPLEX 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 slipht amount of protein 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 administered. If these occur, treatment with Phot hhow PLEX hist 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.
- During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor anti-3 body 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

 $D_{\rm spite}^{\rm l}$ 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

- 1. BIGGS R., MACFARLANE R.G.: Treatment of Haemophilia and other Coagulation Disorders. Blackwell, Oxford (1966)
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IMMUNO LTD Arctic House, Rye Lane, Dunton Green, Nr. Sevenoaks, Kent TN 14 5HB Tel.: Sevenoaks (0732) 58101 & 50342 Manufactured by ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.

Production Division of

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Prothromplex[™] P.O.M. Rartial Prothrombin Complex (Human)

Beoduct Licence Nos. 0215/0006/7/8

公平、古田田田

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 dunors 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, b^{*} 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 precations, the risk of transmission of homologous serum hepatitis can only be lessened and not completely ruled out their france scale to no one obtains at least a 60-fold concentration of the coagulation.

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 contains at least 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. of the activity of Factor IX is assayed through determination of the Partial promoboplastin Time (PTT).

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

ADMINISTRATION

Pirections 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

* 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.

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.

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 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)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.

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

to 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 everage fresh normal plasma. The Factor IX units are expressed in terms of the 1st International Standard for Blood Coagulation Factor IX. Human, 72/32. MOGTA



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: 1T

зŦ 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. IC in the patient's plasma.

Clinical Manifestation	Therapeutically wanted Minimum Factor IX level -	Initial dose in units Factor IX per kg. body weight	Maintenance cose at intervals of 6 to 12 (24) prs. in units Factor IX per kg. bocy 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 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 PRO-THROMPLEX 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 The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

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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:

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 administered. If these occur, treatment with PNOTHNOMPLEX hist 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.
- Despite the precautions taken, the transmission of homologous serum hepatitis cannot be entirely excluded following the administration of coagulation factors.
- During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor anti-body is a possibility. The time at which such an antibody is produced cannot be predicted and depends neither on the amount of the plas-ma 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. 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 articine using the taken of anticoagulant therapy.

SHELF LIFE AND STORAGE

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

PACKS

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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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PROTHROMPLEX BEBULIN

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SIDE EFFECTS

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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 PROTHROM-PLEX TIM 4 must-be interrupted at once.
- Allergic reactions should be controlled with antihistamines and gluco-
- corticosteroids 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.

- 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 $+2^{\circ}$ and $-8^{\circ}C$ 5. 303

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

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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® TIM 4 prestores state and 8 Partial Prothrombin Complex (Human) * 1908 - 100 Aug

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Sy number of y an appropriate so the PROTHER AREA THE SHORE IS Prothrombin Complex is understood to include the vitamin K, dependent coagulation Factors II, VII, IX and X. en energia esta entre entre a la create an

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 (Stuar-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 concen-tration of Factors IX and X is also reached. PROTHROMPLEX TIM 4 is dis-tributed in packs containing either 500 or 200 units* of Factors II, IX and X

PROTHROMPLEX/TIM 4 is prepared from pooled human plasma. 2019.

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 HBs-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 x 10⁶ infectious units of HIV/ml, did not contain any detectable infectious virus after the product specific steam treatment.

INDICATIONS Same regul

30 (98 Spectore) 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 1.12.03

- 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) and we have a set of the set of th

- 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.).
- 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.
- proversion of the interval of the state of t
- 1 LU: 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.

Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROM-PLEX TIM 4, Factor II. Kend X activity is normalized in the second se

D)

- 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 plasmat take and excerned activity of the sufficient rise of Factors II, IX and X in the

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 K₁ in contrast to PROTHROMPLEX TIM 4 becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K₁ 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. speak ar 4 7 5 fts

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. ಕೆಕೆಯಲ್ಲಿಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಅಗೆ ಸಂಗ್ರೆಯ ಸಂಸ್ಥೆ ಸಂಗ್ರೆಯಿಂಗಿ ಮಾಡಿದ್ದಾರೆ. ಕೆಕೆಯಲ್ಲಿಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಸಂಸ್ಥೆಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಸ್ವಾಯಿಸಿದ್ದರೆ ಸಂಸ್ಥೆಯಲ್ಲಿ ಸಂಸ್ಥೆಯಿಂದ ಸಂಸ್ಥೆಯ ಕೆಕೆಯಲ್ಲಿಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಸ್ವಾಯಿಸಿ ಸಂಸ್ಥೆಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಸ್ವಾಯಿಸಿದ್ದರೆ ಸಂಸ್ಥೆಯಲ್ಲಿ ಸ್ವಾಯಿಸಿದ್ದರೆ. ಸಂಸ್

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.

- Warm the unopened bottle containing solvent to room temperature (max. 37°C).
- Remove the caps from the concentrate and solvent bottles (Fig. A) and disinfect the rubber stoppers of both bottles.
- 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).
- Remove the inner cover taking care not to touch the exposed end. 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.
- Upon complete reconstitution of the concentrate insert the enclosed 7. aeration needle (Fig.F) and any foam will collapse. Remove the aeration needle. . n STREET OF

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 Complex press constraints of the second press of the -0 S ADMINISTRATION *C ·· u en eu Intra ang

- 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). 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 intravenous needle (or the infusion set with a winged adapted back and a set of the set of winged adapter).

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

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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 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 - 360 hours, Factor IX approx. 12 - 30 hours, Factor X approx. 20 - 60 hours) successful results are achieved by repeated administration of PROTHROM-PLEX 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, thus ensuring a complication-free postoperative course. The special advantage of PRO-THROMPLEX 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. 36.52

Patients suffering from acquired haemorrhagic diatheses due to lack of Prothrombin Complex factors may require surgery, liver biopsy or spleno-portography. 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. . <u>1 8</u> . . . Ost Make Hebarin



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SIDE EFFECTS

Side effects are rarely observed during treatment with PROTHROMPLEX TIM 4 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 PROTHROM-PLEX TIM 4 must be interrupted at once.

Allergic reactions should be controlled with antihistamines and gluco-corticosteroids 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

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ÖŞTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H. Production Division of

IMMUNO AG Vienna Austria

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PROTHROMPLEX[®] TIM 4 Partial Prothrombin Complex (Human)

Steam Treated 1 มากลากจาก สารแอกแอก เป็นสารสงคุณ เป็นแสดมสง 2 สาราชอาการสงคุณ และสมสาร เป็นสาราชสงคุณ ของสารสาราช ครั้งเชียงพร้างก็ได้สำคัญการสงการสาราจสงการสาราชคุณ สาราชชาติ เป็นสาราชการสาราจสงการสาราจสงการสาราชคุณ สาราชอาการการสำคัญ เป็นสาราชการสาราชการสาราชคุณ สาราชอาการการสาราชการสาราชการสาราชการสาราชการสาราช ŝ.

Prothrombin Complex is understood to include the vitamin Ky dependent coagulation Factors II, VII, IX and X. The second structure of a second structure of the second seco

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). ۰. . 33

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 concen-tration of Factors IX and X is also reached. PROTHROMPLEXTIM 4 is dis-tributed 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 HBs-antigen and HTLV-III-antibodies.

To inactivate potentially present viral agents the manufacture of PRO-THROMPLEX TIM 4 includes a product specific steam treatment (Steam Treatment Immuno 4). Samples of PROTHROMPLEX TIM 4, which were spiked with 2 x 10⁶ 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-for:A-prothrombinaemia (Factor II deficiency) A for the second of the second o 2. Haemophilia B (Factor IX deficiency)
- Angiohaemophilia B (von Willebrand's Disease with Factor IX 3. deficiency)
- 4. Stuart-Prower Factor deficiency (Factor X deficiency)
- 5. Combined deficiency of Factors II, IX or X.
- Treatment for acquired coagulation disorders
- 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.).
- 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. en the to 10 1 1 1

1 LU. 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.

 Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROM-PLEX TIM 4, Factor II, IX and X activity is normalized. Register of the second seco

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- 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 second se

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 K₁ is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K₁ in contrast to PROTHROMPLEX TIM 4 becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K₁ 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

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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).
- Remove the caps from the concentrate and solvent bottles (Fig. A) and disinfect the rubber stoppers of both bottles.

 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.
- Disconnect the two bottles by removing the needle from the concentrate bottle (Fig. E). Gently agitate or rotate the concentrate bottle to accelerate dissolution.
- 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).

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 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 PROTHROM-PLEX 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 disorders, thus ensuring a complication-free postoperative course. The special advantage of PRO-THROMPLEX 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:

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

- Allergic reactions should be controlled with antihistamines and gluco-corticosteroids 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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Production Division of IMMUNO AG Vienna Austria

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PROTHROMPLEX[®] TIM 2 Partial Prothrombin Complex (Human)

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Steam Treated ture tread effet પ્રાથમિક કે **પ્રાયક** પ્રાપ્ય કરવાયું છે. પ્રાથમિક કે વિદીર સ્વયું છે છે છે છે. ઉ**દારાઈન્સ દ્વાર**ી એ સ્વય છે પ્રાપ્ય કરવાયું છે.

, .**.** . Prothrombin Complex is understood to include the vitamin K, 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). د از ک رود کو مورد

MANUFACTURE AND COMPOSITION

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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 HBs-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 x 10⁶ 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. 2

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:

- Hypo- or A-prothrombinaemia (Factor II deficiency) Haemophilia B (Factor IX deficiency) Angiohaemophilia B (von Willebrand's Disease with Factor IX deficiency) 3.
- deficiency) Stuart-Prower Factor deficiency (Factor X deficiency) Combined deficiency of Factors II, IX or X.
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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. PRO-THROMPLEX TIM 2 normalizes Factor II, IX and X activity.

11.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.

- 3. Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROM-PLEX 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

 $\label{eq:protoconstruct} \begin{array}{l} \mbox{PROTHROMPLEX TIM 2 is to be stored in lyophilised condition and should only be reconstituted immediately before administration. The solution must then be used promptly. Entered vials must not be reused. \end{array}$

- 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.
- 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.
- 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.).
- 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 PRO-THROMPLEX 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, thus ensuring a complication-free postoperative course. The special advantage of PRO-THROMPLEX TIM 2 lies in the fact that by application 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
- 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.
- 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.

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

PACKS

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- 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
- all kit for reconstitution and injection

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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). (Stuart-Prower Factor).

PROTHROMPLEX is prepared from pooled plasma of healthy donors and FROMPLEX is prepared from pooled plasma of nearing doins 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 fest, is permanently excluded from the donor programme. Despite these precautions, the risk of transmission of homologous serum hepatitis can be becaused and not completely ruled out only be lessened and not completely ruled out. traductions (c) =

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. Instance to the factor of the sector of the sector

Treatment for inherited or congenital coagulation disorders

- Hypo- or A-prothrombinaemia (Factor II deficiency)
- Haemophilia B (Factor IX deficiency) Angiohaemophilia B (von Willebrand's Disease with Factor IX 11 1 L 16 3.
- deficiency) o eernanT i 2 Stuart-Prower Factor deficiency (Factor X deficiency) TOW
- Treatment for acquired coagulation disorders lating ant in
- 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 PROTHROM-PLEX, 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", 11.U. can also be defined as the Factor IX activity present in 1 mit 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.

- Severe acute haemorrhages caused by vitamin,K deficiency (genuing vitamin K deficiency or as (for example) a consequence of resorbtion disturbances). Through the administration of PBOTHROMPLEX Factor II, IX and X activity is normalized.
- 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 Factorill, 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. Sec.or

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. 1 301

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. la cimence detains such Nectors CENTOPA Instable

ADMINISTRATION

PROTHROMPLEX must be dissolved immediately before injection using the amount of solvent provided. and the set 1.1.4.2

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Directions for Reconstitution of a Solution for Injection $\frac{2\pi^{2}}{2}$

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- 1. Warm solvent to room temperature.
- 2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles. - C - F $\tau_{1,n}$
- 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): and the solvent post of the solvent
- 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 ben the interval
- 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:
- 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.



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. SHELF LIFE AND STORAGE

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DOSAGE

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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; stand s

In cases of inherited or congenital coagulation disorderschigh 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 bleeding, hort 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 protein overloading of the patient is excluded even awith 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 consumption of the coagulation factors has been previously interrupted by Heparin.

OSTERRED FISCHES INSTITUT TOP HOMOOR VARE GESMICH SIDE EFFECTS Side effects are rarely observed during treatment with PROTHROMPLEX

though the following reactions may occur: 2 - 0760 may

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PROTHROMPLEX®

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Partial Prothrombin Complex (Human)

Prothrombin Complex is understood to include the vitamin K₁ 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 becaused and not completely used out? 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) Angiohaemophilia B (von Willebrand's Disease with Factor IX .3. deficiency)
- Stuart-Prower Factor deficiency (Factor X deficiency)
 Combined deficiency of Factors II, IX or X.

Treatment for acquired coaquilation 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.
- Neo-natal haemorrhages, especially when the mother is under oral anticoagulant treatment. Through the administration of PROTHROM-PLEX, Factor II, IX and X activity is normalized.
- . The activity in International Units (I.U.) Factor IX is expressed in terms of the relevant 2 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", 11.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.
- 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 K₁ is recommended to stimulate synthesis of these coagulation factors in the liver. However, with this, it has to be pointed out that vitamin K₁ in contrast to PROTHROMPLEX becomes effective only some hours following intravenous administration. As the intravenous administration of vitamin K₁ 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.
- 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

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.
- 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.



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 X 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 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:

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 1X 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

least 50-fold concentration as compared to fresh plasma. 1 mg protein contains 0.85 to 2.5 1.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 (L.³) 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:

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:

1.500 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 inter-ruption of substitution treatment.

Nild 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 106.

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%	2040%	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.U. Factor IX (according to WHO standard) corresponds to the activity of Factor IX present in 1 ml of fresh average human plasma

of fresh average human plasma.
 ² 1 I.U. heparin according to WHO standard.

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	Plasma level increase %				60%
10	200	300	400	500	600
. 15	300	450	600 -	750	900
20	400	600	800	1000	1200
C 70% 25 0 1985	500	750	1000	1250	1500
10 TOD 30 . 5 . 10 . 5	600	900	1200 :	1500	.1800
35	700	1050	1400	1750	2100
40 40	800	1200	1600	3 2000	2400
45	900	1350	1800	2250	2700
50	1000	1500	2000	2500	3000
	11,00	1650	2200	2750	3300
60	1200	1800	2400	3000	3600
65	1300	1950	2600	3250	3900
70	1400	2100	- 2800	3500	- 4200
75 s s s s	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

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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%	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

1. 1.4

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.
- 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).
- 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.
- Disconnect the two bottles by removing the needle from the concentrate bottle (fig. E). Gently agitate or rotate the concentrate bottle to accelerate dissolution.
- 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 o injection: 2 ml/min.) inject the solution intravenously with the enclosec 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 a 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

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BEBULIN TIM 2

- R/C vial containing 200 IU of lyophilized Factor IX
 R/C vial containing 10 mt 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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ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H. Production Division of IMMUNO AG Vienna Austria

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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 and the second 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 and the second and with REFERENCES ARONSON D. L.: Factor IX Complex. Seminars in Thrombosis and Hemoslasis (1), VI: 28 - 43 (1979) BESSER H. Sur Substitutionstherapie der Koagulopathien. Infusionstherapie und Kinische Ernährung – Forschung und Praxis. 1 (6): 327 – 334 (1974)
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Production Division of

IMMUNO AG Vienna Austria

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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

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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.* 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.*) 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

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:

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 HBs-antigen by Radio Immune Assay (RIA) and found non-reactive.

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 alle a thair a Haemophilia B Congenital or acquired Factor IX deficiency with Factor IX inhibitor. Acquired Factor IX deficiency DNTRAINDICATIONS

CONTRAINDICATIONS

Suspected consumption coagulopathy: administration of BEBULIN TIM 4 is recommended only after elimination of the underlying consumption disorder. Sugar 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 inter-ruption of substitution treatment.

Mild reactions can be managed with antihistamines; severe reactions require immediate intervention. In patients with a history of hyper-sensitivity 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 106. 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.

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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%	34 days or until adequate wound healing
Life threatening haemorrhage: e.g. Intracraniat, 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.

11.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 of the last state to the state of the second

		T		Calman Calman	
Bodyweight	20%	Plasm 30%	a level incre 40%	ase %	60%
10 ^{8 10} 10	200	300	400	500	600
15 .	300	450	600	750	900
20	400	600	. 800	. 1000.	1200
25 m shire	500	750	.1000	1250	1500
5 - 1 PR-30 - 35. 5	C1600 - 1	🧈 900 and	- 1200	1500	1800
35	700	1050: 1	1400	1750	2100
40	800	1200	1600	2000	2400
51 11 45 14 B	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

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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. 1.022.02

Surgery	Preoperative Factor IX level	Postoperative Factor IX leve		
Minor surgery (e.g. dental extractions)	40%	40% 20—40%	Day of operation until adequate wound healing	
Major surgery	60%	60% 40% ·	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. 1.3.4

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 Badose 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%. 14.41 51

In case of vitamin K deficiency, apartfrom 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 and Public and Holestitemane, on the

Additional Instructions

2704153154 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).
- Remove the caps from the concentrate and solvent bottles (fig. A) and 2. disinfect the rubber stoppers of both bottles.
- The enclosed transfer needle (double-ended needle) is protected by З. 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.
- 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.
- 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.