MEDICINES ACTS 1968 AND 1971
APPLICATION FOR PRODUCT LICENCE ON EXPIRY OF EXISTING LICENCE (REVIEW/RENEWAL)

1. Name(s) of product: PROPLEX FACTOR IX COMPLEX (HUMAN)

Particulars of existing licence:

(i) Number	(ii) Date first granted	(iii) Date of Expiry
PL/ 0116/0049	OCTOBER 15,1976	OCTOBER 15,1981

2. Full name and address of licence holder:
TRAVENOL LABORATORIES LTD.,
CAXTON WAY,
THETFORD,
NORFOLK, IP24 3PW

3. Trading style to be shown on licence (if different from 2 above)
AS ABOVE

4. Role of licence holder: (place tick in appropriate box(es))
(i) as person responsible for composition of product manufactured in UK ☐
(ii) as person who imports or procures its importation ☑
(iii) as person who first sells or supplies it as a medicinal product in UK ☑
(iv) as person responsible for placing a proprietary medicinal product on the market in UK ☑

5. Activities for which licence is required: (place tick in appropriate box(es))
(i) selling or supplying product in the UK ☑
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK ☑
(iii) importing or procuring the importation of the product ☑
(iv) other (specify) EXPORTING THE PRODUCT ☑

6. Scientific evidence attached (description with number of pages)
(i) pharmaceutical 8 pages + APPENDICES 7 PAGES
(ii) medical 5 pages

7. I/We* apply for review/renewal of the licence as at 1 above in order that a product licence be granted in respect of the product to which the Product Particulars in Part 1A refer, and in accordance with the other particulars annexed; the said licence to be subject to the following provisions:

7.1 Except where they conflict with the licence particulars, all the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of the Medicines Act 1968.

7.2 The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the licensing authority.

7.3 The specification of the constituents and the specification and standards of the finished product shall be in accordance with the information contained in or furnished in connection with this application.

7.4 The product is to be manufactured only in accordance with the methods set out or furnished in connection with this application.

8. I/We* certify that the information supplied with this application gives an accurate account of the product.

Signature GRO-C Date 26th October 1983

Capacity in which signed SENIOR SCIENTIFIC OFFICER

Name and address and telephone number for communications:

A. M. CAMERON, B.SC., M.I.BIOL.,
TRAVENOL LABORATORIES LTD., CAXTON WAY, THETFORD,
NORFOLK IP24 3PW. TEL. GRO-C

*Delete as appropriate

Issued by: DHSS (Medicines Division)
Market Towers
1 Nine Elms Lane
Vauxhall, London SW8 5NQ

Dd. 8329833 5000 Sets FM(P)Ltd. 10/82

Official use only

A 1

Form MLA 201R PART 1A

PRODUCT PARTICULARS

1. Number of Product:

PL 0116/0049

Name of Product: PROPLEX FACTOR IX COMPLEX (HUMAN)

Official use only

2. Description of Pharmaceutical form:
THE PRODUCT IS A DRIED CONCENTRATE OF CLOTTING FACTORS II (PROTHROMBIN), VII (PROCONVERTIN), IX (PTC, ANTIHAEMOPHILIC FACTOR B) AND X (STUART-POWER FACTOR). IT IS PACKAGED WITH A SUITABLE VOLUME OF WATER FOR INJECTIONS PH EUR FOR RECONSTITUTION INTO A FORM FOR ADMINISTRATION TO HUMANS.

Official use only

Official use only

3. Legal status (place tick in appropriate box):

Official use only

Prescription	✓	Pharmacy		General Sales	

Official use only

D 1

4. Active Constituents:

Official use only	Name	Specification Reference	Quantity/Dose Unit or % quantity		Overage	**
			quantity	unit		
	FACTOR IX (P.T.C.) (MINIMUM ACTIVITY)	WHO300		IU		
	FACTOR II (PROTHROMBIN) (MINIMUM ACTIVITY)	HSE	90	AU		
	FACTOR X (STUART-PROWER) (MAXIMUM ACTIVITY)	HSE960		AU		

1) Please enter constituent as actual substance included in the formulation, eg. as salt not base where applicable.
2) Where specification is unofficial please insert HSE in Specification Reference column.
3) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
4) Column headed 'Overage' to be completed for GSL products only.
5) For GSL products only please tick in column headed ** if identity tests are carried out on each batch.
6) Please photocopy page if more space for constituents is required.

C 1

5. Uses, directions for use, and route(s) of administration:

PROPLEX FACTOR IX COMPLEX (HUMAN) IS A STERILE, DRIED CONCENTRATE CONTAINING THE CLOTTING FACTORS II (PROTHROMBIN), VII (PROCONVERTIN), IX (PTC, ANTIHAEMOPHILIC FACTOR B) AND X (STUART-POWER FACTOR). THE PRODUCT IS PREPARED FROM POOLED HUMAN PLASMA AND CONTAINS NO PRESERVATIVE.

PROPLEX FACTOR IX COMPLEX (HUMAN) IS INDICATED FOR THE TREATMENT OF FACTOR IX DEFICIENCY (HAEMOPHILIA B, CHRISTMAS DISEASE) AND CONGENITAL DEFICIENCIES OF FACTORS II OR X. THE INTRAVENOUS ADMINISTRATION OF THIS PREPARATION IS INTENDED TO PREVENT OR CONTROL BLEEDING EPISODES IN SUCH PATIENTS.

IT MAY ALSO BE USEFUL IN THE TREATMENT OF SOME HAEMORRHAGIC CONDITIONS OF THE NEWBORN AND IN COAGULATION DISORDERS ASSOCIATED WITH HEPATIC DISEASE.

PROPLEX FACTOR IX COMPLEX (HUMAN) IS FOR ADMINISTRATION BY INTRAVENOUS INJECTION. WHEN RECONSTITUTION IS COMPLETE, THE SOLUTION SHOULD BE ADMINISTERED WITHIN THREE HOURS. THE SOLUTION, AFTER RECONSTITUTION, SHOULD BE ADMINISTERED AT ROOM TEMPERATURE USING AN ADMINISTRATION SET WITH A FILTER. IT SHOULD BE INFUSED SLOWLY, AT A RATE OF APPROXIMATELY 2 TO 3 ML PER MINUTE. THIS FLOW RATE SHOULD BE REDUCED IF THE PULSE RATE INCREASES SIGNIFICANTLY.

Official use only

B 1

6. Recommended doses and dosage schedules:

Distinguish between adults and children and between different clinical uses

THE AMOUNT OF PROPLEX FACTOR IX COMPLEX (HUMAN) REQUIRED TO RESTORE NORMAL HAEMOSTASIS VARIES WITH THE CIRCUMSTANCES AND WITH THE PATIENT. THE FOLLOWING FORMULAE CAN BE USED TO CALCULATE THE APPROXIMATE DOSE REQUIRED FOR A GIVEN EFFECT OR THE APPROXIMATE RESPONSE FROM A GIVEN DOSE, BASED ON FACTOR IX UNITS:

Offici use of

A. UNITS REQUIRED = 0.6 X BODY WEIGHT (KG) X DESIRED INCREASE (% OF NORMAL)

B. EXPECTED INCREASE (% OF NORMAL) = $\frac{\text{UNITS ADMINISTERED}}{\text{0.6 X BODY WEIGHT (KG)}}$

IN PREPARATION FOR, AND FOLLOWING SURGERY, LEVELS ABOVE 25%, MAINTAINED FOR AT LEAST A WEEK AFTER SURGERY, ARE SUGGESTED. LABORATORY CONTROL TO ASSURE SUCH LEVELS IS RECOMMENDED. TO MAINTAIN LEVELS ABOVE 25% FOR A REASONABLE TIME, EACH DOSE SHOULD BE CALCULATED TO RAISE THE LEVEL TO 40 OR 50 % OF NORMAL. FOR DEFICIENCIES OF FACTORS II AND X, USING THE PROCEEDING FORMULAE FOR FACTOR IX CORRECTION, 6 UNITS OF ANY OF THE FACTORS PER KG OF BODY WEIGHT WOULD BE EXPECTED TO PRODUCE AN INCREASE OF ABOUT 10% (OF NORMAL) IN THE PLASMA LEVEL OF THAT FACTOR.
IF INHIBITORS OF ANY DEFICIENT FACTOR APPEAR TO BE PRESENT, SUFFICIENT ADDITIONAL DOSAGE TO OVERCOME THE INHIBITOR WOULD BE NEEDED.

FOR MAINTENANCE OF AN ELEVATED LEVEL OF A DEFICIENT FACTOR, DOSAGE MAY BE REPEATED AS OFTEN AS NEEDED.

Official use only

7. Contra-indications:

PROPLEX FACTOR IX COMPLEX (HUMAN) IS CONTRAINDICATED IN PATIENTS WITH DISSEMINATED INTRAVASCULAR COAGULATION OR FIBRINOLYSIS.

B 2

8. Precautions:

1. IF SIGNS OF INTRAVASCULAR COAGULATION OCCUR, WHICH INCLUDE CHANGES IN BLOOD PRESSURE AND PULSE RATE, RESPIRATORY DISTRESS, CHEST PAIN AND COUGH, THE INFUSION SHOULD BE PROMPTLY STOPPED

2. IDENTIFICATION OF THE DEFICIENCY AS ONE OF FACTOR II, IX OR X IS ESSENTIAL BEFORE ADMINISTRATION OF PROPLEX FACTOR IX COMPLEX (HUMAN).

3. PROPLEX FACTOR IX COMPLEX (HUMAN) CONTAINS A SAMLL AMOUNT OF HEPARIN AS A STABILISING AGENT. THE MAXIMUM AMOUNT PRESENT IS 1.0 UNIT PER ML OF RECONSTITUTED MATERIAL. THIS AMOUNT DOES NOT AFFECT THE CLINICAL USEFULNESS OF THE CONCENTRATE IN MODERATE DOSAGE.

9. Warnings:

PROPLEX FACTOR IX COMPLEX (HUMAN) IS PREPARED FROM LARGE POOLS OF HUMAN PLASMA. SUCH PLASMA MAY CONTAIN THE CAUSATIVE AGENT OF VIRAL HEPATITIS. ALTHOUGH EACH UNIT OF THE PLASMA HAS BEEN FOUND TO BE NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HBSAG) BY RADIOIMMUNOASSAY, THE PRODUCT HAS NOT BEEN SUBJECTED TO ANY TREATMENT KNOWN TO DIMINISH THE RISK OF TRANSMITTING HEPATITIS. THE PRODUCT SHOULD, THEREFORE, BE USED ONLY WHEN THE NEED FOR ITS EXPECTED EFFECT OUTWEIGHS THE HEPATITIS RISK ASSOCIATED WITH ITS USE. SPECIAL CONSIDERATION SHOULD BE GIVEN TO THE USE OF THIS COMPLEX IN NEWBORNS WHERE A HIGHER MORBIDITY AND MORTALITY MAY BE ASSOCIATED WITH HEPATITIS, AND IN PATIENTS WITH PRE-EXISTING LIVER DISEASE.

Official use only

10. Name of manufacturer(s) of the product, and site(s) of manufacture:

PROPLEX FACTOR IX COMPLEX
HYLAND DIVISION,
TRAVENOL LABORATORIES INC.,
4501 COLORADO,
LOS ANGELES,
CALIFORNIA 90039

AND/OR N.V. TRAVENOL LABORATORIES, S.A.,
BOULEVARD D'HOURAING,
7860-LESSINES,
BELGIUM.

WATER FOR INJECTIONS PH. EUR.
PHARMA HAMELN,
3250 HAMELN 1, (AFERDE),
WEST GERMANY.

AND/OR N.V. TRAVENOL LABORATORIES S.A.,
BOULEVARD D'HOURAING,
7860-LESSINES,
BELGIUM.

Applicant's signature GRO-C Date 26th October 1983

Form MLA 201R

PART 1B

Further Information

1. Assembler(s):

HYLAND DIVISION,
TRAVENOL LABORATORIES INC.,
4501 COLORADO,
LOS ANGELES,
CALIFORNIA 90039

AND/OR N.V. TRAVENOL LABORATORIES, S.A.,
BOULEVARD D'HOURAING,
7860-LESSINES,
BELGIUM.

2. Importer:

TRAVENOL LABORATORIES LTD.,
CAXTON WAY,
THETFORD,
NORFOLK, IP24 3PW

3. List other countries of registration:

WEST GERMANY,
SPAIN,
UNITED STATES

4. Site and Arrangements for Quality Control (in the UK, and, where applicable, on importation):

QUALITY CONTROL WILL BE CARRIED OUT AT THE PLACE OF MANUFACTURE. THE LICENCE HOLDER WILL BE RESPONSIBLE FOR DECIDING IF A BATCH IS OF ACCEPTABLE QUALITY FOR RELEASE.

5. Type of container(s), pack size(s), shelf life and storage precautions:

	Container Size	Unit	*Official use only*
30 ML GLASS VIAL OF PROPLEX FACTOR IX CONCENTRATE 30 ML GLASS VIAL OF WATER FOR INJECTIONS PH. EUR. FOR RECONSTITUTION	30	ML	

SHELF LIFE IS 24 MONTHS

PRODUCT SHOULD BE STORED BETWEEN 2° AND 8°C AND MAY BE STORED AT ROOM TEMPERATURE FOR UP TO FOUR WEEKS WITHIN DATING PERIOD.

Note: Please tabulate data in space allowed
Where applicable enter unit as MG, GM, ML, LT for litre etc.
Where coded entry is ambiguous leave as text.

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FORM MLA 201R

6. Other constituents:

Official use only	Name	Specification Reference	mod	Quantity/Dose Unit or % quantity: quantity	unit	**
	HEPARIN, SODIUM	USP	QS			
	SODIUM CHLORIDE	USP		0.21	G	
	SODIUM CITRATE DIHYDRATE	USP		0.18	G	
	POLYETHYLENE GLYCOL	NF	QS			
	CALCIUM PHOSPHATE	NF	QS			
	SODIUM HYDROXIDE	NF	QS			
	HYDROCHLORIC ACID	NF	QS			
	WATER FOR INJECTIONS	EP	TO	30	ML	

Applicant's signature GRO-C Date 26th October, 1983

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
2) Where specification is unofficial please insert HSE in Specification Reference column.
3) Please complete modifier column marked mod. as follows:
   Insert TO if final volume cannot be expressed as a complete quantity.
   Insert ND for substances not detectable in the final formulation, eg. solvents.
   Insert QS if quantity not fixed, eg. for substances used to adjust pH.
4) Where quantity is expressed as a percentage please insert WW, WV, etc. as appropriate in unit column. Please do not include percentage sign.
5) For GSL products only please tick in column headed ** if identity tests are carried out on each batch.
6) Please photocopy page if more space for constituents is required.

PHARMACEUTICAL SUMMARY PART II

1. CHEMISTRY AND PHARMACY

1.1 PRODUCTION AND QUALITY CONTROL OF THE PHARMACEUTICAL FORM

1.1.1 FORMULATION

Each 30 ml vial contains:

a) Factor IX Complex

Factor IX (Plasma Thromboplastin)	Minimum 900 I.U.
Factor II (Prothrombin)	Minimum 90 A.U.
Factor X (Stuart-Prower Factor)	Not more than 960 A.U.
Factor VII (Proconvertin)	Not more than 3,900 A.U.

b) Water for Injections to 30 mls

c) Heparin, Sodium (a maximum of 30 units)

d) Sodium Citrate Dihydrate 0.18 g

e) Sodium Chloride 0.21 g

f) Polyethylene Glycol (a maximum of 60 mg)

g) Calcium Phosphate (a maximum of 3 mg)

h) Sodium Hydroxide as required for pH adjustment

i) Hydrochloric Acid as required for pH adjustment.

1.1.2 METHOD OF MANUFACTURE OF DOSAGE FORM

PROPLEX Factor IX Complex is prepared by large scale fractionation of human plasma. The fraction known as Cohn IV_1, is suspended and extracted with 0.9% sodium chloride while maintaining the pH at approximately 6.0. The pH is subsequently adjusted to 7.2 with sodium hydroxide. The extracted suspension is decanted or centrifuged with the precipitate being discarded. The pH of the supernate is determined and, if necessary adjusted to 7.2. Tribasic calcium phosphate (5 grams/L of solution) is then added to the supernatant to adsorb the coagulation factors associated with the prothrombin complex. After thorough mixing, the calcium phosphate is recovered by centrifugation and the supernatant is discarded.

The adsorbed prothrombin complex coagulation factors are eluted from the tricalcium phosphate with 0.1M sodium citrate. The calcium phosphate is removed by centrifugation and discarded. The pH of the remaining supernatant is determined and adjusted to pH 7.0 with hydrochloric acid. Polyethylene glycol 3350 is added to the supernatant to provide a 15% weight to volume concentration. Following centrifugation, the precipitate is descarded and the pH of the supernatant is adjusted to 7.0 and sodium heparin is added to a concentration of 500 units/liter of supernatant. Polyethylene glycol is again added to provide a 20% weight to volume concentration. After centrifugation, the supernatant is adjusted to pH 5.2 with hydrochloric acid. The precipitated prothrombin complex is collected by centrifugation. The precipitate is resuspended in heparinised citrated saline containing 0.02M sodium citrate, 0.72% sodium chloride and 1.5 units/ml of heparin. The pH is adjusted to 7.0 with sodium hydroxide.

The product is clarified and sterilised by passage through membrane filters of graduated pore size. The filtrate is filled into sterile vials, frozen, lyophilised, stoppered and capped aseptically.

These final container vials are submitted to tests required by product specifications.

1.1.3 SPECIFICATION OF CONSTITUENTS

a) Factor IX Complex Manufactured from Source Plasma (Human)

Source Plasma (Human) is collected in plasmapheresis centres operated in accordance with procedures specified by the Bureau of Biologics, United States Food and Drug Administration. Each unit of plasma used meets the requirement for that product as defined in the United States Code of Federal Regulations (21CFR640, Subpart G). All containers and collection devices used in the processing of Source Plasma (Human) are sterile, pyrogen-free, non-toxic and compatible with the contents. Sealed plastic bottles or plasma collection bags are constructed so as to exclude micro-organisms and maintain a sterile system. Each unit of Source Plasma (Human) is tested for the presence of hepatitis B surface antigen (HBsAg) using third generation reagents licensed by the Bureau of Biologics. Source Plasma (Human) is frozen at -20°C or colder following collection and is stored at such temperatures until shipped. Temperature during shipment is maintained at -5°C or colder. Further details are given in the Travenol Master File RA1002 - Source Plasma (Human).

b) Water for Injections

Meets requirements of U.S.P. or Ph. Eur.

c) Heparin Sodium

Meets requirements of U.S.P.

d) Sodium Citrate Dihydrate

Meets requirements of U.S.P. or Ph. Eur.

e) Sodium Chloride

Meets requirements of U.S.P. or Ph. Eur.

f) Polyethylene Glycol

Meets requirements of N.F. or Belgian Ph.

g) Calcium Phosphate

Meets requirements of N.F. or Ph. Eur.

h) Sodium Hydroxide

Meets requirements of N.F. or B.P.

i) Hydrochloric Acid

Meets requirements of N.F. or Ph. Eur.

1.1.4 TESTS CARRIED OUT ON EACH BATCH OF EACH CONSTITUENT

In the absence of a Manufacturer's Certificate of Analysis each constituent is tested in accordance with the relevant Pharmacopoeia Monograph.

In addition each constituent is tested for non-pyrogenicity in accordance with U.S.P. or Ph. Eur. methodology.

1.1.5 TESTS CARRIED OUT DURING MANUFACTURE

The following tests may be carried out during manufacture:

a) pH measurement

b) Protein content

c) Ionic strength

d) Temperature

1.1.6 FINISHED PRODUCT SPECIFICATION

1.1.6.1 Chemical Specification

a) pH.

The product is reconstituted with Water for Injections.

The limits are 6.0 to 7.6

b) Moisture

The limit is a 3% maximum.

c) Solubility

The material must dissolve completely within 5 minutes (at room temperature).

d) Total Protein

The limit is a maximum of 15g/l of reconstituted material.

e) Total Calcium Content

The limit is a maximum of 100 mg/l of reconstituted material.

f) Polyethylene Glycol Content

The limit is a maximum of 2g/l of reconstituted material.

g) Factor IX Activity (Plasma Thromboplastin Component)

The limits is a minimum of 300 Factor IX units per vial.

h) Factor II Activity (Prothrombin)

The limit is a minimum of 90 Factor II units per vial.

i) Factor VII Activity (Proconvertin)

The limit is a maximum of 3,900 Factor VII units per vial.

j) Factor X Activity (Stuart Prower Factor)

The limit is a maximum of 960 Factor X units per vial.

k) Identity

Human protein - positive

Animal protein - negative

l) Isoagglutinin Titre

Natural Anti-A or Anti-B titre - maximum of 1:16

Immune Anti-A or Anti-B titre - maximum of 1:32.

m) Thrombin Assay

Not more than 0.010 units/ml immediately after reconstitution.

Not more than 0.010 units/ml after 3 hours at room temperature after reconstitution.

n) Thrombogenic Assay (Non-Activated Partial Thromboplastin Time)

The average of duplicate determinations must be 100 seconds or greater for the 1:100 dilution. In addition each replicate determination of the 1:100 dilution must be 100 seconds or greater.

o) Heparin Assay

The limit is a maximum of 1.0 Units/ml.

p) Hepatitis B Surface Antigen

The product must be non-reactive for HBsAg as determined by third generation reagents.

q) General Safety (Toxicity)

The product must produce no significant symptoms when injected intraperitoneally into mice and guinea pigs.

1.1.6.2 Physical Specification

a) Fill Volume

The limits are 30 to 32 mls.

1.1.6.3 Test Methods

References are to Travenol Manual of Test Procedures File RA1001.

Test	Method	
pH	11-83A	
Moisture	7-00A	
Total Protein	7-79A	
Calcium Content	9-83A	
Polyethylene Glycol Content	88-22A	(Principal)
	7-74A	(Alternative)
Factor IX Activity	3-77A	
Factor II Activity	3-75A	
Factor VII Activity	4-92A	
Factor X Activity	88-06A	
Protein Identity	6-60A	
Isoagglutinin Titre	12-18A	
Thrombin Assay	87-95A	
Thrombogenic Assay	4-73A	
Heparin Assay	4-10A	
Hepatitis B Surface Antigen	87-88B	
General Safety	6-08A	

1.1.7 SHELF LIFE

The shelf life of the product is 2 years from date of manufacture.

1.1.8 TESTS CARRIED OUT ON EACH BATCH OF THE PRODUCT

1.1.8.1 Testing

Each batch will be tested to ensure that the product conforms to Section 1.1.6 (Finished Product Specification).

1.1.8.2 Batch Analysis

Analytical results are shown in tabulated form in Appendix I.

1.1.9 MICROBIOLOGICAL TESTING

The finished product is tested for:

a) Sterility

Test procedure of the European Pharmacopoeia or United States Pharmacopoeia.

b) Pyrogenicity

Test procedure of the European Pharmacopoeia or United States Pharmacopoeia.

1.1.10 CONTAINER

The product is supplied in single use glass vials which meet the specification for Type I Clear Glass Vials of the U.S.P.

1.2 SUPPORTING EVIDENCE FOR SECTION 1.1

1.2.1 STABILITY DATA

Stability data which support the proposed shelf life are shown in tabulated form in Appendix II.

MEDICAL/SCIENTIFIC SUMMARY

2. HUMAN PHARMACOLOGICAL STUDIES, CLINICAL TRIALS, CLINICAL EXPERIENCE

Prothrombin complex concentrates (Factor IX Complexes) have been the subject of several major reviews covering the pharmacology and clinical use. As the published literature is so extensive this summary does not follow the order given in the Guidelines of MAL58 Revised. A bibliography of major reviews on the pharmacology and therapeutic uses of the product is given and the specific indications contained in the Data Sheet and Direction Insert are referenced.

2.1 Major References on Prothrombin complex concentrates and appropriate Clinical Uses.

1. Aledort, L.M., Goodnight, S.H.
Hemophilia Treatment: Its Relationship to Blood Products in Progress in Haematology (XII).
ed Brown, E.B., New York 1981.

2. Bayer, W.L., Shea, J.D., et. al.
Excision of a Pseudocyst of the Hand in a Hemophiliac (PTC-Deficiency).
J. Bone and Joint Surgery, 51-A, (7), 1423-1427, 1969.

Summary: A pseudocyst was successfully excised from the hand of a plasma thromboplastin component (IX) deficient patient. The coagulation defect was controlled by infusions of IX-rich plasma fraction (Hyland).

3. Bick, R.L., Schmalhorst, W.R. et. al.
Prothrombin Complex Concentrate: Use in Controlling the Haemorrhagic Diathesis of Chronic Liver Disease.
Digestive Diseases, 20, (8), 741-749, 1975.

Summary: A prothrombin complex concentrate (Proplex) was used in attempts to control life-threatening haemorrhage in 4 patients with chronic liver disease. The population manifested profuse bleeding from varices and/or haemorrhagic gastritis; 3 had Laennec's cirrhosis and 1 had postnecrotic cirrhosis from childhood hepatitis. In all patients the complex was given in amounts needed to raise the prothrombin (factor II) level to approximately 100% of normal. In all 4 cases the prothrombin time and prothrombin complex factors approached normal within 1-2 hours after beginning the infusion. In all patients bleeding ceased with correction of the clotting status. One patient rebled several hours after completing the infusion. In several patients, increases in factors V and VIII were noted following infusion of the

concentrate. A further unexpected finding was a spontaneous increase in factors II and IX at 3 days postinfusion. Prothrombin complex concentrate appears to be useful in controlling the haemorrhage of chromic liver disease when used alone or in combination with other modalities to correct specific haemostatic defects; however, patients may be expected to rebleed when the effect of the concentrate wears off. Its use, therefore, should probably be restricted to those patients who are to undergo corrective surgery of the bleeding point once haemostasis is achieved.

4. Biggs, R (ed).
The Treatment of Haemophilia A and B and von Willebrand's Disease.
Oxford, Blackwell 1978.

5. Chandra, S, Brummelhvis, H.G.J.
Prothrombin Complex Concentrates for Clinical Use.
Vox Sang, 41, 257-273, 1981.

6. Coan, M.H., Fournel, M.A., et. al.
Properties of Commerical Factor IX Concentrates.
Ann. N.Y. Acad. Sci., 370, 731-746, 1981.

7. Gilchrist, G.S., Ekert, H, et. al.
Evaluation of a New Concentrate for the Treatment of Factor IX Deficiency.
N.E.J.M., 280, 291-295, 1969.

Summary: A commercially prepared plasma concentrate (Hyland) was administered in six infusions to four patients with factor IX deficiency. All showed a distinct rise in the factor IX level. On the basis of the preliminary data a dose of 2 factor IX units per kilogram of body weight could be expected to produce a 1 per cent rise in the factor IX level. Larger doses may be necessary in the actively bleeding patient. No serious side effects were observed. The increased factor IX concentration and the relatively low protein content of the material greatly reduces the possibility of precipitating circulatory overload while still achieving haemostatic factor IX levels.

8. Kline, S.N., Lewis, J.H., et.al.
Multiple Extractions in Haemophilia B - use of PTC (Factor IX) Concentrate - report of case.
J. Oral Surgery, 28, 292-294, 1970.

Summary: Multiple extractions and traumatic dental manipulation were accomplished in a factor IX-deficient patient treated with a high potency factor IX concentrate (Hyland). Haemostatis and healing were completely satisfactory. The judicious use of such fractions offers great hope in the future therapy of patients suffering from haemophilia B.

9. Masure, R., Myllyla, G. et. al.
Preparation and Use of Coagulation Factors VIII and IX for Transfusion.
European Public Health Committee, Strasbourg 1980.

10. Menache, D.
Prothrombin Complex Concentrates: Clincal Use.
Ann. N.Y. Acad. Sci., 370, 747-756, 1981.

11. Menache, D.
Factor IX Concentrates.
Thrombos. Diathes. Haemorrh., 33, 600-605, 1975.

12. Menache, D., Roberts, H.R.
Summary Report and Recommendations of the Task Force Members and Consultants.
Thrombos. Diathes. Haemorrh., 33, 645-647, 1975.

Summary: Recommendations on the uses and potential hazards of Factor IX Concentrates are given. The high risk of hepatitis B transmission and the potential thrombogenicity of Factor IX concentrates are discussed. A suggested list of indications and contraindications for Factor IX concentrate use is given.

13. Shanbrom, E.
Clinical Experience with Factor IX Concentrates (Prothrombin Complex) Haemophilia and New Haemorrhagic States. 27-30.
Univ. North Carolina Press, 1970.

14. White, G.C., Lundblad, R.L. et.al.
Prothrombin Complex Concentrates: Preparation, Properties and Clincal Uses.
Current Topics in Haematology, 2, 203-244, 1979.

15. Zauber, N.P., Levin J.
Factor IX Levels in Patients with Haemophilia B (Christmas Disease) Following Transfusion with Concentrates of Factor IX or Fresh Frozen Plasma.
Medicine, 56, (3), 213-224, 1977.

Summary: The variables that may affect the level and duration of response of patients with haemophilia B (Christmas disease) to transfusion were examined. A total of 49 transfusion episodes and 171 previously reported transfusions were evaluated.

Mean calculated initial increase of Factor IX levels (%/unit (U) of procoagulant activity infused/kg) was 0.82 ± 0.09% (mean ± S.E.) in previously reported cases and 1.01 ± 0.13% in patients, after transfusion of concentrate; but only 0.50 ± 0.11% after fresh frozen plasma (FFP). Response was not altered by acute haemorrhage, baseline Factor IX levels, or body weight. Proplex® (Hyland) and Konyne® (Cutter) produced similar responses. Following transfusion, the disappearance curve was biphasic. The mean $T_{\frac{1}{2}}$ for the second component was 27.6 hrs, but the direct $T_{\frac{1}{2}}$ was only 6.4 ± 1.0 hr.

Regardless of common clinical variables, increase of Factor IX following transfusion of American concentrates is 1.0% (or 0.01 U)/U administered/kg. Appropriate frequency of transfusion depends upon an understanding of the biphasic disappearance of Facotr IX. Importantly, the initial frequency of transfusion therapy should be based on a direct $T_{\frac{1}{2}}$ of only 6 to 8 hrs.

2.2 Specific Indications for the Clinical Use of PROPLEX Factor IX Complex (Human)

Clinical Indications for the use of PROPLEX Factor IX Complex (Human)	References (cited in Section 2.1) which detail clinical uses
1. For the treatment of Factor IX Deficiency (haemophilia B, Christmas disease)	2,5,7,8,9,10,12,13,14,15
2. For the treatment of congenital deficiency of Factors II or X.	3,5,9,10,12,14
3. For the treatment of some haemorrhagic conditions of the newborn.	5,12,14

4. For the treatment of coagulation disorders associated with hepatic disease.	3,5,14

2.3 Adverse Reactions to Clinical Use of Factor IX Complex

The risk of thrombosis is present with the administration of Factor IX Complex particularly in patients with pre-existing liver disease and the product is contraindicated in patients with disseminated intra-vascular coagulation or fibrinolysis.	5,9,14
The risk of hepatitis B and hepatitis non-A non-B is present as PROPLEX. Factor IX Complex (Human) is prepared from large pools of human plasma. Therefore the product should only be used when its expected effect out-weighs the hepatitis risk associated with its use. Special consideration should be given to the use of Factor IX Complex in newborns where a higher morbidity and mortality may be associated with hepatitis.	5,9,11,14

CONTAINER LABEL

Proplex
Factor IX Complex (Human)

HYLAND

30 ml size, dried

Reconstitute with 30 ml of Water for Injections Ph. Eur.

Administer intravenously at room temperature. Administer within 3 hours after reconstitution is complete. If a gel forms on reconstitution, the preparation should not be used.

The reconstituted material contains not more than 1.5 g of total protein and not more than 0.20 g of polyethylene glycol per 100 ml. Stabilised with heparin, not more than 1.0 unit per ml of reconstituted material. Contains no preservative.

Warning: The risk of transmitting hepatitis is present.

Directions and dose: See accompanying direction sheet.

STORE BETWEEN 2° and 8°C (35° and 46°F). Protect from light.

This vial contains
I.U. of Factor IX activity
Units of Factor II activity
Units of Factor X activity.

LOT

EXP. DATE (5°C)

IX

Distributed by
TRAVENOL LABORATORIES LTD
Thetford, Norfolk, England

PL 0116/0049

30-4D-00-500C

POM

DATA SHEET

Further Information
Representative material from each lot, after reconstitution as for use, has been found nonreactive for hepatitis B surface antigen (HBsAg) using a solid phase radioimmunoassay technique licensed by the National Center for Drugs and Biologics, U.S. Food and Drug Administration.
Each lot of PROPLEX Factor IX Complex (Human) is assayed for the Activated Clotting Factors (Kingdon Time) in seconds. This is a measure of the thrombogenic nature of the concentrate.
Further information is available upon request.
Refer to product direction sheet for more detailed information on PROPLEX Factor IX Complex (Human).

Product Licence Number
0116/0049

Date of Preparation
October 1982

TRAVENOL LABORATORIES LTD.,
Thetford, Norfolk, IP24 3SE, England
Telephone Thetford (0842) 4581

30-5D-00-540B

DATA SHEET

HYLAND

Proplex Factor IX Complex (Human)

Presentation
PROPLEX Factor IX Complex (Human) is a sterile, dried, concentrate containing the clotting Factors II (prothrombin), VII (proconvertin), IX (PTC, antihaemophilic factor B) and X (Stuart-Prower factor). The product is prepared from pooled human plasma and contains no preservative.

Uses
PROPLEX Factor IX Complex (Human) is indicated for the treatment of Factor IX deficiency (haemophilia B, Christmas disease) and congenital deficiencies of Factors II or X. The intravenous administration of this preparation is intended to prevent or control bleeding episodes in such patients.
It may also be useful in the treatment of some haemorrhagic conditions of the newborn and in coagulation disorders associated with hepatic disease.

Dosage and Administration
Each vial of PROPLEX Factor IX Complex (Human) is labelled with the number of Factor IX (International Units), Factor II and Factor X Units which it contains, each unit being defined as the respective activity present in 1 ml of average, normal, pooled human plasma less than one hour old (100 % level).
The amount of PROPLEX Factor IX Complex (Human) required to restore normal haemostasis varies with the circumstances and with the patient. The following formulae can be used to calculate the approximate dose required for a given effect or the approximate response from a given dose, based on Factor IX Units:

A. Units required = 0.6 x body weight (kg) x desired increase (% of normal)

B. Expected increase (% of normal) = $\frac{\text{units administered}}{0.6 \times \text{body weight (kg)}}$

In preparation for, and following surgery, levels above 25 %, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25 % for a reasonable time, each dose should be calculated to raise the level to 40 or 50 % of normal.
For deficiencies of Factors II and X, using the proceeding formulae for Factor IX correction, 6 units of any of the factors per kg of body weight would be expected to produce an increase of about 10 % (of normal) in the plasma level of that factor.
If inhibitors of any deficient factor appear to be present, sufficient additional dosage to overcome the inhibitor would be needed.
For maintenance of an elevated level of a deficient factor, dosage may be repeated as often as needed.
PROPLEX Factor IX Complex (Human) is for administration by intravenous injection. When reconstitution is complete, the solution should be administered within three hours. The solution, after reconstitution, should be administered at room temperature using an administration set with a filter. It should be infused slowly, at a rate of approximately 2 to 3 ml per minute. This flow rate should be reduced if the pulse rate increases significantly.

Contraindications, Warnings, Etc

Contraindications

PROPLEX Factor IX Complex (Human) is contraindicated in patients with disseminated intravascular coagulation or fibrinolysis.

Warning

PROPLEX Factor IX Complex (Human) is prepared from large pools of human plasma. Such plasma may contain the causative agent of viral hepatitis. Although each unit of the plasma has been found to be nonreactive for hepatitis B surface antigen (HBsAg) by radioimmunoassay, the product has not been subjected to any treatment known to diminish the risk of transmitting hepatitis. The product should, therefore, be used only when the need for its expected effect outweighs the hepatitis risk associated with its use. Special consideration should be given to the use of this complex in newborns where a higher morbidity and mortality may be associated with hepatitis, and in patients with pre-existing liver disease.

Precautions

1. If signs of intravascular coagulation occur, which include changes in blood pressure and pulse rate, respiratory distress, chest pain and cough, the infusion should be promptly stopped.
2. Identification of the deficiency as one of Factor II, IX or X is essential before administration of PROPLEX Factor IX Complex (Human).
3. PROPLEX Factor IX Complex (Human) contains a small amount of heparin as a stabilising agent. The maximum amount present is 1.0 unit per ml of reconstituted material. This amount does not affect the clinical usefulness of the concentrate in moderate dosage.

Adverse Reactions

As with other plasma products, pyrogenic reactions manifested by chills and fever may occasionally be seen, particularly when large doses of PROPLEX Factor IX Complex (Human) are administered.
If the concentrate is infused too rapidly, one may observe flushing, increased pulse rate and decreased blood pressure. Stopping the infusion allows the symptoms to disappear promptly. With all but the most reactive individuals, the infusion may be resumed at a slower rate.
The risk of thrombosis is present with the administration of Human Factor IX Complex.

Pharmaceutical Precautions

PROPLEX Factor IX Complex (Human) should be stored under ordinary refrigeration (2° to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent vial may occur.
Protect from light.
PROPLEX Factor IX Complex (Human) may be stored at room temperature for time periods up to four weeks.
If a gel forms on reconstitution, the preparation should not be used.
The administration set and any reconstituted material not immediately injected should be discarded.

Legal Category

Prescription Only Medicine.

Package Quantities

PROPLEX Factor IX Complex (Human) is supplied in 'kit' form, consisting of a 30 ml vial of Factor IX Complex concentrate, a 30 ml vial containing Water for Injections Ph.Eur. for reconstitution of the dried concentrate, a double-ended needle for transfer of the water and a filter needle.

DIRECTION SHEET

HYLAND

Proplex
Factor IX Complex (Human)

Warning: This is a potent drug with potential hazards. For maximal safety and efficacy, carefully read and follow directions below.

Description

PROPLEX Factor IX Complex (Human)* is prepared from pooled normal human plasma. It contains, in concentrated form, clotting Factors II (prothrombin), VII (proconvertin), IX (PTC, antihaemophilic factor B) and X (Stuart-Prower factor); other proteins are present in small amounts. The product also contains a small amount of heparin, 1.0 unit or less per ml of reconstituted material, as a stabilising agent, and not more than 1.5 g of total protein and not more than 0.20 g of polyethylene glycol per 100 ml of reconstituted material.

Each lot of PROPLEX Factor IX Complex (Human) is assayed and labelled for Factors II, IX and X. The amount of Factor IX present is reported in International Units. Each lot of material is also assayed for Activated Clotting Factors (Kingdon Time), in seconds. This is an in vitro assay, performed to assess the thrombogenic nature of the concentrate.[1]

Representative material from each lot, after reconstitution as for use, has been found nonreactive for hepatitis B surface antigen (HBsAg) using a solid phase radioimmunoassay technique licensed by the National Center for Drugs and Biologics, U.S. Food and Drug Administration. The significance of a nonreactive test result with Factor IX concentrate has not been established. Therefore, the product should continue to be considered to carry a risk with respect to hepatitis.

Indications

PROPLEX Factor IX Complex (Human) is intended for use in the treatment of Factor IX deficiency (haemophilia B, Christmas disease) and congenital deficiencies of Factors II or X. The intravenous administration of this preparation is intended to prevent or control bleeding episodes due to deficiencies of these factors.

It may also be useful in some haemorrhagic conditions of the newborn and in coagulation disorders associated with hepatic disease.

Contraindications

The use of PROPLEX Factor IX Complex (Human) is contraindicated in patients with disseminated intravascular coagulation or fibrinolysis.

Warnings

This product is prepared form large pools of human plasma. Such plasma may contain the causative agents of viral hepatitis. Although each unit of the plasma has been found to be nonreactive for hepatitis B surface antigen (HBsAg) by radioimmunoassay, the product has not been subjected to any treatment known to diminish the risk of transmitting hepatitis. The product should, therefore, be used only when the need for its expected effect outweighs the hepatitis risk associated with its use. Special consideration should be given to the use of this complex in newborns where a higher morbidity and mortality may be associated with hepatitis, and in patients with pre-existing liver disease.

Precautions

If signs of intravascular coagulation occur, which include changes in blood pressure and pulse rate, respiratory distress, chest pain and cough, the infusion should be promptly stopped. In general, the risk of enhancing intravascular coagulation may be reduced by not attempting to raise the patient's Factor IX level to more than 50 % of normal. If the need exists to raise the patient's Factor IX level higher than 50 % of normal, the physician should monitor the infusion of material to detect signs and symptoms of intravascular coagulation.

Identification of the deficiency as one of Factor II, IX or X is essential before administration of this concentrate. No benefit may be expected from this product in treating other deficiencies.

PROPLEX Factor IX Complex (Human) contains a small amount of heparin as a stabilising agent. The maximal amount present is 1.0 unit per ml of reconstituted material. This amount does not affect the clinical usefulness of the complex in moderate dosage.

Adverse Reactions

As with other plasma products, pyrogenic reactions manifested by chills and fever may occassionally be seen (2-5) particularly when large doses of PROPLEX Factor IX Complex (Human) are administered.

If PROPLEX Factor IX Complex (Human) is infused too rapidly, one may observe flushing, increased pulse rate and decreased blood pressure. Stopping the infusion allows the symptoms to disappear promptly. With all but the most reactive individuals, the infusion may be resumed at a slower rate.

The risk of thrombosis is present with the administration of Factor IX Complex (Human).

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Dosage and Administration
Each vial of PROPLEX Factor IX Complex (Human) is labelled with the number of International Factor IX Units which it contains, and also, the number of Factor II and X units which it contains. Each of these units is defined as the respective activity present in 1 ml of average normal pooled human plasma less than one hour old (100 % level).

Dosage
The amount of PROPLEX Factor IX Complex (Human) required to restore normal haemostasis varies with the circumstances and with the patient. Dosage depends on the degree of deficiency and the desired haemostatic level of the deficient factor.
The following formulae can be used to calculate the approximate dose required for a given effect or the approximate response from a given dose, in relation to Factor IX units:

(1) Units required = 0.6 x body weight (kg) x desired increase (% of normal)

(2) Expected increase (% of normal) = $\frac{\text{units administered}}{0.6 \times \text{body weight (kg)}}$

Thus, if a man weighing 60 kg had zero Factor IX initially, and it is desired to raise his plasma level to 25 %, the suggested dose by formula (1) would be:

Units required = 0.6 x 60 x 25 = 900

In Factor IX deficiency, it may be necessary to raise the patient's Factor IX level to only 10 % of normal to control haemarthrosis. Using Formula (1) above, a 60 kg patient with no Factor IX would require 360 Units to reach such a level. In preparation for, and following surgery, levels above 25 %, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25 % for a reasonable time, each dose should be calculated to raise the level to 40 or 50 % of normal. See Precautions.
For deficiencies of Factors II and X it has been suggested that levels below 10 % of normal are likely to lead to bleeding. 6 However, another authority 7 has suggested the following as "haemostatically effective" levels: Factor II - 40 %, Factor X - probably 15 - 20 %.
Using the formulae given above for Factor IX correction, 6 units of any of the factors per kg of body weight would be expected to produce an increase of about 10 % (of normal) in the plasma level of that factor. If inhibitors of any deficient factor appear to be present, sufficient additional dosage to overcome the inhibitor would be needed.

For maintenance of an elevated level of a deficient factor, dosage may be repeated as often as needed. Clinical studies suggest that relatively high levels may be maintained by daily or twice-daily doses, while the lower effective levels may require injections only once every two or three days. A single dose may be sufficient to stop a minor bleeding episode.8-11

Laboratory Tests
Since the dosage of PROPLEX Factor IX Complex (Human) with respect to Factor IX is calculated on the basis of its potency, frequent laboratory tests to monitor the effectiveness of treatment are usually unnecessary.
A number of partial thromboplastin time (PTT) tests may be performed at intervals, beginning a few hours after infusion, to determine any additional need for correction of the deficiency involved. The necessity for these tests is dependent upon the severity of bleeding, the presence or absence of Factor IX inhibitor, and subsequent signs of clinical improvement.

Reconstitution
1. Bring PROPLEX Factor IX Complex (Human) and Water for Injections Ph. Eur. to room temperature.
2. Remove caps from PROPLEX Factor IX Complex (Human) and diluent vials to expose central portions of rubber stoppers.
3. Cleanse stoppers with antiseptic solution.
4. Remove protective covering from one end of double-ended needle, using care not to touch exposed end. Insert exposed needle through diluent stopper.
5. Remove protective covering from other end of double-ended needle, using aseptic technique as above. Invert diluent vial over the upright PROPLEX Factor IX Complex (Human) vial, then rapidly insert free end of needle through the vial stopper at its centre. Vacuum in PROPLEX Factor IX Complex (Human) vial will draw in diluent.
6. Disconnect the two vials by removing needle from PROPLEX Factor IX Complex (Human) vial stopper. Agitate or rotate vial until all the concentrate is dissolved. Be sure that the concentrate is completely dissolved; otherwise, active material may be removed by the filter. If a gel forms on reconstitution, the preparation should not be used.

Administration
Administration of PROPLEX Factor IX Complex (Human) is by the intravenous route. When reconstitution of the concentrate is complete, its infusion should commence within 3 hours. However, it is recommended that the infusion begin as promptly as is practicable. The concentrate should be

HYLAND

infused slowly, at a rate of approximately 2 - 3 ml per minute. The flow rate should be reduced if the pulse rate increases significantly. The material should not be below room temperature during infusion.

A. Intravenous Drip Infusion

1. Follow directions for use accompanying the set being used. Make certain administration set contains an adequate filter.
2. If the patient is to receive more than one vial of PROPLEX Factor IX Complex (Human), administration of each subsequent vial should begin within 3 hours following its reconstitution. The administration set may be removed from the empty vial and inserted into the full vial, provided care is taken to avoid entrapment of air in the set. This practice avoids loss of concentrate in the set and makes additional venepunctures unnecessary.
3. When administration of the concentrate is finished, it is desirable to connect the administration set to a bottle of 0.9 % w/v sodium chloride solution and flush into the vein any concentrate remaining in the set. Avoid introduction of air into the tubing.
4. Discard administration set after use. Also discard any unused reconstituted concentrate.

B. Intravenous Syringe Injection

1. After reconstituting the concentrate as described under Reconstitution, attach the filter needle to a plastic syringe and insert the needle through the vial stopper.
2. Inject air and aspirate the reconstituted material into the syringe.
3. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously at a rate not exceeding 3 ml per minute.
4. If the patient is to receive additional vials of PROPLEX Factor IX Complex (Human), the same syringe may be refilled through filter needles; this practice lessens the loss of concentrate.

Storage

PROPLEX Factor IX Complex (Human) should be stored under ordinary refrigeration (2° to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent vial may occur. Protect from light.
PROPLEX Factor IX Complex (Human) may be stored at room temperature for time periods up to four weeks.

How Supplied

PROPLEX Factor IX Complex (Human) is supplied with a suitable volume of Water for Injections Ph. Eur., a double-ended needle and a filter needle.

References

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PL 0116/0049

30-5D-00-520D

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TRAVENOL LABORATORIES LTD.,
Thetford, Norfolk, England

*Manufactured under U.S. Patents Nos. 3,415,804 and 3,560,475.

CARTON

30 ml size, dried code KD-060-212

Proplex
Factor IX Complex (Human)

Contains
one 30 ml vial of dried Factor IX Complex (Human),
one 30 ml vial of Water for Injections Ph. Eur.
one double-ended needle and one filter needle.

Warning: This is a potent drug with potential hazards.
For maximal safety and efficacy, carefully read
and follow enclosed direction sheet.

STORE BETWEEN 2° and 8°C (35° AND 46°F).
Avoid freezing, which might damage diluent vial.
Protect from light.

PL 0116/0049.

POM

IX

Distributed by
TRAVENOL LABORATORIES LTD.,
Thetford, Norfolk, England

-00-560C

Proplex
Factor IX Complex (Human)

code KD-060-212

HYLAND

HYLAND

HYLAND

Read warnings and direction sheet before use.

For intravenous administration.

Warning: The risk of transmitting hepatitis is present, although this product is derived from plasma which was nonreactive when tested for hepatitis B surface antigen (HBsAg) by radioimmunoassay.

The reconstituted material contains not more than 1.5 g of total protein and not more than 0.20 g of polyethylene glycol per 100 ml. Stabilised with heparin, not more than 1.0 unit per ml of reconstituted material. Contains no preservative.

Administer within three hours after reconstitution is complete. If a gel forms on reconstitution, the preparation should not be used.

This lot contains per vial
I.U. of Factor IX activity
Units of Factor II activity
Units of Factor X activity

LOT
EXP. DATE (5°C)

30-6D-00-560C

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Thetford,

APPENDIX I

BATCH ANALYSIS TABLE 1

Product: PROPLEX Factor IX Complex (Human)
Container, volume: Glass vial - 30 ml

Analysis	Limits	Batch No. 0581X102A
Factor II	90 Units/vial Min	240
Factor VII	3,900 Units/vial Max	3180
Factor IX	300 Units/vial Min	480
Fctor X	960 Units/vial Max	450
Thrombin	0.010 Units/ml Max	<0.003
Thrombogenicity	100 Secs minimum for 1:100 Dilution	157.4
Total Protein	15 g/l Max	4.7
pH	6.0 - 7.6	6.9
Calcium	100 mg/l Max	6
Polyethylene Glycol	2 g/l Max	0.2
Solubility	5 mins Max	1.0
Moisture	3% Max	1.5
Identity	Satisfactory	Satisfactory
Isoagglutinin Titre	Natural Anti A or Anti B - Pass	Pass
	Immune Anti A or Anti B - Pass	Pass
HBsAg	Negative	Negative
Heparin	1.0 Units/ml Max	0.5
Sterility	Satisfactory	Satisfactory
Pyrogenicity	Satisfactory	Satisfactory

BA/PROPLEX

BATCH ANALYSIS TABLE 2

Product: PROPLEX Factor IX Complex (Human)
Container, volume: Glass vial - 30 ml

Analysis	Limits	Batch No. 0581X105A
Factor II	90 Units/vial Min	240
Factor VII	3,900 Units/vial Max	2100
Factor IX	300 Units/vial Min	420
Fctor X	960 Units/vial Max	420
Thrombin	0.010 Units/ml Max	<0.003
Thrombogenicity	100 Secs minimum for 1:100 Dilution	197.9
Total Protein	15 g/l Max	4.3
pH	6.0 - 7.6	7.0
Calcium	100 mg/l Max	10
Polyethylene Glycol	2 g/l Max	0.2
Solubility	5 mins Max	<1.0
Moisture	3% Max	1.6
Identity	Satisfactory	Satisfactory
Isoagglutinin Titre	Natural Anti A or Anti B - Pass	Pass
	Immune Anti A or Anti B - Pass	Pass
HBsAg	Negative	Negative
Heparin	1.0 Units/ml Max	0.5
Sterility	Satisfactory	Satisfactory
Pyrogenicity	Satisfactory	Satisfactory

RA/PROPLEX

BATCH ANALYSIS TABLE 3

Product: PROPLEX Factor IX Complex (Human)
Container, volume: Glass vial - 30 ml

Analysis	Limits	Batch No. 0581X107A
Factor II	90 Units/vial Min	240
Factor VII	3,900 Units/vial Max	3600
Factor IX	300 Units/vial Min	570
Fctor X	960 Units/vial Max	450
Thrombin	0.010 Units/ml Max	<0.003
Thrombogenicity	100 Secs minimum for 1:100 Dilution	169.8
Total Protein	15 g/l Max	5.7
pH	6.0 - 7.6	7.0
Calcium	100 mg/l Max	8
Polyethylene Glycol	2 g/l Max	0.3
Solubility	5 mins Max	<1.0
Moisture	3% Max	1.7
Identity	Satisfactory	Satisfactory
Isoagglutinin Titre	Natural Anti A or Anti B - Pass	Pass
	Immune Anti A or Anti B - Pass	Pass
HBsAg	Negative	Negative
Heparin	1.0 Units/ml Max	0.6
Sterility	Satisfactory	Satisfactory
Pyrogenicity	Satisfactory	Satisfactory

BA/PROPLEX

APPENDIX II

STABILITY TABLE 1

Product:	**PROPLEX Factor IX Complex (Human)**
Container, volume:	**Glass vial - 30 ml**
Batch Number:	**0581 C208A**
Temperature:	**5°C**

Analysis	Limits	Initial	6 Mo.	12 Mo.	24 Mo.
Factor II	90 Units/vial Min	120	213	-	229
Factor VII	3,900 Units/vial Max	1422	1102	1197	1476 (36 MO)
Factor IX	300 Units/vial Min	390	372	-	435
Factor X	960 Units/vial Max	482	390	348	409 (30 MO)
Thrombin	0.010 Units/ml Max	<0.001	<0.001	-	<0.001
Thrombogenicity	100 Secs minimum for 1:100 Dilution	203	135	-	241
Heparin	1.0 Units/ml Max	0.6	-	-	0.7
pH	6.0 - 7.6	6.9	6.9	6.9	6.9 (30 MO)
Pyrogens	Pass	Pass	-	-	Pass
General Safety	Pass	Pass	-	-	Pass
Solubility	5 mins Max	<1	<1	-	<1
Sterility	Pass	Pass	-	-	Pass
Moisture	3% Max	0.8	-	-	3.0 (36 MO)

STABILITY TABLE 2

Product:	**PROPLEX Factor IX Complex (Human)**
Container, volume:	**Glass vial - 30 ml**
Batch Number:	**0581 C208A**
Temperature:	**25°C**

Analysis	Limits	Initial	12 MO.	24 MO.
Factor II	90 Units/vial Min	120	162	225
Factor VII	3,900 Units/vial Max	1422	-	1132 (30 MO)
Factor IX	300 Units/vial Min	390	318	417
Factor X	960 Units/vial Max	482	-	386 (30 MO)
Thrombin	0.010 Units/ml Max	<0.001	<0.001	<0.001
Thrombogenicity	100 Secs minimum for 1:100 Dilution	203	238	232
pH	6.0 - 7.6	6.9	-	6.9 (30 MO)
Solubility	5 mins Max	<1	<1	<1
Sterility	Pass			
Moisture	3% Max	0.8	-	6.0 (36 MO)

STABILITY TABLE 3

Product:	**PROPLEX Factor IX Complex (Human)**
Container, volume:	**Glass vial - 30 ml**
Batch Number:	**0581 C209A**
Temperature:	**5°C**

Analysis	Limits	Initial	6 Mo.	12 Mo.	36 Mo.
Factor II	90 Units/vial Min	120	250	-	213
Factor VII	3,900 Units/vial Max	1497	1332		1584
Factor IX	300 Units/vial Min	360	378	-	315
Factor X	960 Units/vial Max	417	308	-	345
Thrombin	0.010 Units/ml Max	<0.001	<0.001	-	<0.001
Thrombogenicity	100 Secs minimum for 1:100 Dilution	239	189	-	216
Haparin	1.0 Units/ml Max	0.5	-	-	0.6
pH	6.0 - 7.6	7.0	7.0	7.0	6.9
Pyrogens	Pass	*Fail	-	-	Pass
General Safety	Pass	Pass	-	-	Pass
Solubility	5 mins Max	<1	<1	-	<1
Sterility	Pass	Pass	-	-	Pass
Moisture	3% Max	0.6	-	-	3.3

*The batch was known to be pyrogenic after filling and was therefore used for stability testing purposes.

Other parameters are valid for indicating stability.

SD/0581 C209A

Product:	**PROPLEX Factor IX Complex (Human)**
Container, volume:	**Glass vial - 30 ml**
Batch Number:	**0581 C209A**
Temperature:	**25°C**

Analysis	Limits	Initial	18 MO.	36 MO.
Factor II	90 Units/vial Min	120	190	172
Factor VII	3,900 Units/vial Max	1497	-	1632
Factor IX	300 Units/vial Min	360	375	261
Factor X	960 Units/vial Max	417	-	303
Thrombin	0.010 Units/ml Max	<0.001	<0.001	<0.001
Thrombogenicity	100 Secs minimum for 1:100 Dilution	239	228	207
pH	6.0 - 7.6	7.0	-	6.9
Solubility	5 mins Max	<1	<1	<1
Sterility	Pass			
Moisture	3% Max	0.6	-	6.0