Response to Questions Raised at the Inquiry into Contaminated Blood and Blood Plasma Products

1b. Examples of Warnings Issued with Coagulation Factor Concentrates (warnings not highlighted)

Peter R Foster, BSc MSc PhD CS CSci CEng FIChemE
Protein Fractionation Centre
Scottish National Blood Transfusion Service
21 Ellen’s Glen Road, Edinburgh, EH17 7QT.

September 2007.
Introduction

During my evidence to the Inquiry on 29th August 2007, I agreed to provide examples of warning literature held by SNBTS. A number of examples are attached. These are listed below. Original documents are available for inspection if necessary. Two copies are provided for the inquiry, one (version 1a) in which the warnings are highlighted and another (version 1b) in which the copies are unmarked.

1. SNBTS Documents

(a) **Product Licence Applications (extracts)**

Extracts from the initial product licence applications submitted by SNBTS for coagulation factor concentrates are attached. These extracts demonstrate that warnings concerning hepatitis were included in licence applications that were submitted to the Medicines Control Agency. The following documentation is attached:

SNBTS Factor VIII concentrate, unheated: PLA of 30th March 1978.
SNBTS Factor IX concentrate, unheated: PLA of 30th October 1978.

(b) **SNBTS Product leaflets**

Copies are attached of leaflets supplied with the following SNBTS products:

Factor VIII concentrate, unheated
Factor VIII concentrate, dry-heated at 68°C
Factor IX concentrate, unheated
Factor IX concentrate, dry-heated at 80°C

(c) **SNBTS vial labels**

Copies are attached of vial labels for the following SNBTS products

Factor VIII concentrate, unheated
Factor VIII concentrate, dry-heated at 68°C
Factor IX concentrate, unheated

(c) **SNBTS Carton**

Copies are attached of the carton in which vials were packaged:

Factor VIII concentrate, unheated (side, front & top)
Factor VIII concentrate, unheated (side, back & base)
2. Commercial Company Product Data Sheets (miscellaneous)

Copies of product information leaflets provided with a number of commercial products are attached. A number of USA leaflets are included as well as those used in UK for comparative purposes.

Copies of the following leaflets are attached:

(a) Alpha Therapeutic

Factor VIII concentrate, unheated (Profilate) – USA leaflet (1979)
Factor VIII concentrate, (Profilate heat-treated) – UK data sheet (1986)

(b) Baxter (Hyland/Travenol)

Factor VIII concentrate, unheated (Hemofil) – UK data sheet (1977)
Factor VIII concentrate, unheated (Hemofil) – USA leaflet (1975).

(c) Cutter (Miles/Bayer)

Factor VIII concentrate, unheated (Koâte) – USA leaflet (1978)
Factor VIII concentrate, dry-heated at 68°C (Koâte-HT) – UK data sheet (1985)
Factor IX concentrate, unheated (Konyne) – USA leaflet (1978)

(d) Immuno Ltd

Factor VIII concentrate, unheated (Kryobulin) – UK data sheet (1979)
Factor IX concentrate, unheated (Prothromplex) – UK data sheet (1979)
1. Examples of Warnings in Documents

Provided by SNBTS
1. Name of product: Human Antihaemophilic Factor: Factor VIII (Lyophilised)

2. Full name and address of proposed licence holder:
   Committee of Management
   Scottish Health Service
   Common Services Agency
   Trinity Park House
   South Trinity Road
   EDINBURGH
   EH5 3PY

3. Trading style in which the proposed licence holder is to be known:
   Scottish National Blood Transfusion Service
   Protein Fractionation Centre
   21 Ellen's Glen Road
   EDINBURGH
   EH17 7QT

4. Role of proposed licence holder:
   (i) as person responsible for composition of product manufactured in UK
   (ii) as person responsible for the manufacture or assembly of the product for sale or supply in the UK
   (iii) as person responsible for the testing of the product

5. Activities for which the licence is required:
   (i) storing, buying, possessing, offering for sale, hiring, letting, transferring or supplying the product

6. Applicants own reference no.: PLA 004/77

7. Details of earlier applications: None

8. To cover supply of the product manufactured before the grant of the licence:

9. Scientific Evidence:
   (i) Chemistry and Pharmacy
   (ii) Experimental and Biological Studies
   (iii) Clinical Trials

10. Number of pages of supplementary information:

11. I/We apply for the grant of a product licence to the proposed licence holder named above in respect of the product(s) to which the Product Particulars on Page 1 refer and in accordance with the other particulars annexed: the said licence to be for a period of five years and subject to the following provisions—
   1. all the standard provisions applicable to product licences under regulations for the time being in force under Section 47 of the Medicines Act 1968.
   2. The product shall not be recommended to be used for any purpose other than those specified in the Product particulars as Doses, 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.
   3. The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.
   4. The product is to be manufactured only in accordance with the methods set out in this application or furnished in connection with it.
   5. The number of the licence shall appear on all containers or packages in which the product is packed and on any package inserts or accompanying literature.

30th April 1978

Signature:
State capacity in which signed: Committee.
2.1 Name of Product: Human Antihaemophilic Factor: Factor VIII (Lyophilised)

2.2 Pharmaceutical form: The product is a dry powder or white friable solid dispensed as a single dose unit for intravenous injection after resolution using "water for injection", and is in a form suitable for administration to human beings.

2.3 Active constituents: Human blood coagulation factor VIII as expressed in international units from the extant British standard for factor VIII activity. The product, should dissolve at room temperature to produce a clear or slightly opalescent solution in 15 minutes when treated as described in the British Pharmacopoeia (1973) page 65.

2.4 Use: The material is intended for the repair of deficiencies of the coagulation factor VIII as encountered in persons having the condition known as Haemophilia A. It is intended for administration by the intravenous route.

2.5 Recommended dose and dosage schedule: There is no recommendation for dosage beyond that required to achieve adequate haemostasis in the patient as judged by clinical manifestation or by laboratory assessment.

2.6 Contra-indications, Precautions and Warnings: There are no contra-indications. Warnings include storage below 5°C, reconstitution by addition of pyrogen free distilled water, the material should not be infused if a gel forms on solution and should be discarded if it is not used within three hours of preparation of solution. Product may carry the risk of transmitting serum hepatitis.

2.7 Method of retail sale or supply: The product is distributed free of charge to the Haemophilia Treatment Centres through the agency of Regional Transfusion Centres.

2.8 Manufacturer of dosage form: Scottish National Blood Transfusion Service, Protein Fractionation Centre 21 Ellen's Glen Road EDINBURGH EH17 7QT

Applicant's reference number (as on page 1) 004/77
Applicant's signature

LIT.001.4493
APPENDIX II

PROPOSED PACKAGE LEAFLET INSERT
HUMAN ANTIHAEMOPHILIC FACTOR - FACTOR VIII CONCENTRATE (LYOPHILISED)

Description

This preparation, which is rich in coagulation factor VIII is recovered from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from\(^1,2\) controlled cryoglobulin precipitate made from plasma volumes requiring up to 1 200 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using reverse passive haemagglutination or radioimmunoassay and the preparation has also been examined by more searching techniques applied in at least two laboratories external to the laboratory of manufacture. Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded.

Factor VIII concentrate contains natural blood group antibodies derived from the plasma of origin. The amounts present are not significant except in circumstances where very large volumes are being administered over a long period (as in major surgery). In such circumstances patients of the blood groups A, B or AB should be observed for evidence of intravascular haemolysis.

Storage

Factor VIII concentrate should be stored in the dark at temperatures below 5\(^\circ\)C. Maintenance of potency is best achieved at temperatures below -35\(^\circ\)C but at least 90% of the stated potency should be recoverable after 12 months storage at temperatures between 2 and 5\(^\circ\)C. It should not be stored for prolonged periods in the range of +1 to -1\(^\circ\)C and the accompanying vial of water for reconstitution cannot be stored safely below 0\(^\circ\)C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and addition to the dry powder using a syringe and employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

After approximately five minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained or directly to the Protein Fractionation Centre.

Where/
Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.

**Administration**

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophiliac status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrhage, an infusion of 1 international unit per kilogramme body weight will produce an average increase of about 2 IU/100 ml of plasma. Presence of abnormally low response in absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma. Intervals between administrations are usually 4, 8, 12 or 24 hours as appropriate.

**Side Effects**

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transitory headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

**References**


Scottish National Blood Transfusion Service
Protein Fractionation Centre
21 Ellen's Glen Road
EDINBURGH
EH17 7QT
### Human Factor IX Concentrate (DE.F.IX)

#### 1.2. Full name and address of proposed licence holder:
Committee of Management  
Scottish Health Service  
Common Services Agency  
Trinity Park House  
South Trinity Road  
EDINBURGH  
EH5 3PY

#### 1.3. Trading style to be shown on licence if different from above:
Scottish National Blood Transfusion Service  
Protein Fractionation Centre  
21 Ellen's Glen Road  
EDINBURGH  
EH17 7QT

#### 1.4. Role of proposed licence holder:
(i) as person responsible for composition of product manufactured in UK.

#### 1.5. Activities for which licence is required:
(1) presenting the manufacture or assembly of the product for sale or supply in the UK.

#### 1.6. Application number reference no. PLA 008/78

#### 1.7. Details of earlier applications: None

#### 1.8. To cover sale and supply of the product manufactured before the grant of the licence:熱EN/BEK

### 1.9. Scientific Evidence:
- (1) Chemistry and Pharmacy Pages  
- (16) Experimental and Biological Studies Pages  
- (111) Clinical Trials Pages

#### 1.10. Number of pages of supplementary information:

#### 1.11. To apply for the grant of a product licence to the proposed holder named above in respect of the product(s) to which the Product Particulars on Page 2 refer and in accordance with the other particulars annexed; the said licence to be for a period of five years and subject to the following provisions -

1. All the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of the Medicines Act 1968.

2. The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars on the form, 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.

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

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

5. The number of the licence shall appear on all containers or packages in which the product is packed and on any package inserts or accompanying literature.

**Signature**

Date: 31st October 1978

[Signature]  
Stamp capacity in which signed.
Product Particulars

2.1 Name of Product: Human Factor IX Concentrate (DE.F. IX)

2.2 Pharmaceutical form: The product is a dry powder or white friable solid dispensed as a single dose unit for intravenous injection after reconstitution using "water for injection", and is in a form suitable for administration to human beings.

2.3 Active Constituents: Human blood coagulation factors II, IX and X expressed in international units from the extant British standard for factor IX activity. The product should dissolve at room temperature to produce a clear or slightly opalescent solution in 5 minutes when treated as described in the British Pharmacopoeia (1973) page 65.

2.4 Use: The material is intended for the repair of deficiencies of the coagulation factor IX as encountered in persons having the condition known as Haemophilia B. It is intended for administration by the intravenous route. It is also used on physician judgement for repair of other acquired deficiencies of factor IX.

2.5 Recommended dose and dosage schedule: There is no recommendation for dosage beyond that required to achieve adequate haemostasis in the patient as judged by clinical manifestation or by laboratory assessment.

2.6 Contra-indications, Precautions and Warnings: Warnings include storage below 5°C, reconstitution by addition of pyrogen free distilled water, the material should not be infused if a gel forms on solution and should be discarded if it is not used within three hours of preparation of solution. Product may carry the risk of transmitting serum hepatitis. There is slight generic risk of diffuse intravascular thrombosis following use of products of this type.

2.7 Method of supply or sale: The product is distributed free of charge to Haemophilia Treatment Centres through the agency of Regional Transfusion Centres.

2.8 Manufacturer of dosage form: Scottish National Blood Transfusion Service Protein Fractionation Centre 21 Ellen's Glen Road EDINBURGH EH17 7QT

Applicant's reference number (as on page 1) 008/78
Applicant's signature

Watt

For the Management Committee
APPENDIX III

PROPOSED PACKAGE LEAFLET INSERT
HUMAN FACTOR IX CONCENTRATE - DE.F.IX

Description

This preparation, which is rich in coagulation factors II, IX and X is recovered from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction by absorption from plasma volumes requiring up to 720 donations of plasma.

All plasma used for preparation of factor IX concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using reverse passive haemagglutination or radioimmunoassay and the preparation has also been examined by more searching techniques applied in at least two laboratories external to the laboratory of manufacture. Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded.

Storage

Factor IX concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below -35°C but at least 90% of the stated potency should be recoverable after 24 months storage at temperatures between 2 and 5°C. It should not be stored for prolonged periods in the range of +1°C to -1°C and the accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and addition to the dry powder using a syringe and employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

After approximately two minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained or directly to the Protein Fractionation Centre.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of one hour following resolution.

Reconstituted/
Reconstituted factor IX concentrate solution should not be stored.

Administration

Factor IX concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids. It may be diluted using saline injection BP but should be administered quickly following dilution.

The actual volume of solution required for any administration depends on the status of the individual patient and the purpose of treatment. Treatment may require to be repeated at varying intervals to maintain the required concentration of factor IX activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects

Complications in the use of factor IX concentrate DE.F.IX are rare. Apart from the general complications of hepatitis products containing concentrations of coagulation factor IX have a well documented reputation for causing diffuse intravascular coagulation or thrombosis at the injection site. Although factor IX concentrate (DE.F.IX) has not been implicated in episodes of this nature the reason for freedom from such side-effect is not known and caution in use is advised; especially in circumstances where the recipient may have liver disease or any acquired deficiency of factor IX.

Heparin

This product does not contain heparin.

Reference

HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII CONCENTRATE

(LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared from frozen indateri human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from controlled cryoglobulin precipitate (1, 2) recovered from plasma volumes requiring up to 4000 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using a radioimmunoassay and the preparation has also been examined by more sensitive techniques applied in at least two laboratories external to the place of manufacture. Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded.

Factor VIII concentrate contains natural blood group antibodies derived from the plasma of origin. The amounts present are not significant except in circumstances where very large volumes are being administered over a long period (as in major surgery). In such circumstances patients of the blood groups A, B or AB should be observed for evidence of intravascular haemolysis.

The reconstituted product contains not more than 60g/l total protein less than 200 m. mol/l sodium ions and not more than 50 m. mol/l citrate ions.

Storage

Factor VIII concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures between 0 and 5°C. The accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and added to the dry powder using a syringe, employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within twenty minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Administration

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophilic status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrhage, an infusion of 1 international unit per kilogramme body weight will produce an average increase of about 2 IU/100 ml of plasma. Presence of abnormally low response in absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma.

Side Effects

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transitory headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

References


Scottish National Blood Transfusion Service,
Protein Fractionation Centre,
21 Ellen's Glen Road,
Edinburgh EH17 7GT.

P.F.C.356 Waddie & Co.

Prod.Lic.3473/0007

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.
HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII CONCENTRATE – HT (LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared from frozen, inactivated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from controlled cryoglobulin precipitate (1, 2) recovered from plasma volumes requiring up to 6000 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using a radioimmunoassay and the preparation has also been examined by more sensitive techniques applied in at least two laboratories.

The product has been heat treated at 60°C for twenty-four hours in the dried state (3) but it cannot be assumed that the product is non-infective.

Factor VIII concentrate contains natural blood group antibodies derived from the plasma of origin. The amounts present are not significant except in circumstances where very large volumes are being administered over a long period (as in major surgery). In such circumstances patients of the blood groups A, B or AB should be observed for evidence of intravascular haemolysis.

The reconstituted product contains not more than 60g/l total protein, not more than 40g/l sucrose, less than 200 m.mol/l sodium ions and less than 50 m.mol/l citrate ions.

Storage

Factor VIII concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below 5°C but at least 90 per cent of the stated potency should be recoverable after 12 months storage at temperatures between 0 and 5°C. The accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and added to the dry powder using a syringe, employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within twenty minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.

Administration

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastic or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have any addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophiliac status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrhage, an infusion of 1 international unit per kilogramme body weight will produce an average increase of about 2 IU/100 ml of plasma. Presence of abnormally low response in absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transient headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

References


Scottish National Blood Transfusion Service
Protein Fractionation Centre
21 Ellen's Glen Road
Edinburgh EH17 7QT

P.F.C.55L, Waddie & Co. 5/4/85 Prod Lic.3473/0007
HUMAN FACTOR IX CONCENTRATE—DE.F.IX

Description
This preparation, which is rich in coagulation factors II, IX and X is recovered from frozen inactivated human plasma by the Scottish Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction by adsorption from plasma volumes requiring up to 6000 donations of plasma.

All plasma used for preparation of factor IX concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using radioimmunoassay and the preparation has also been examined by more searching techniques applied in at least two laboratories external to the place of manufacture. Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded.

The reconstituted product contains 300 i.u Factor IX, not less than 200 i.u Factor II and not less than 200 i.u Factor X. It contains not more than 2 g/l total protein, less than 50 m.mol/l citrate ions and less than 50 m.mol/l phosphate ions.

Storage
Factor IX Concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below —30°C but at least 90 per cent of the stated potency should be recoverable after 12 months storage at temperatures between 2 and 5°C. It should not be stored for prolonged periods in the range of +1°C to +10°C and the accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Indications
Human Factor IX Concentrate—DE.F.IX is issued for treatment of congenital factor IX deficiency (Haemophilia B).

Resolution from the Dry State
If the material has been stored below the freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and addition to the dry powder using a syringe and employing aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within ten minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained or directly to the Protein Fractionation Centre.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of three hours following resolution. Reconstituted Factor IX Concentrate solution should not be stored.

Administration
Factor IX Concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids. It may be diluted using sodium chloride injection BP but should be administered quickly following dilution.

The actual volume of solution required for any administration depends on the status of the individual patient and the purpose of treatment. Treatment may require to be repeated at varying intervals to maintain the required concentration of factor IX activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects
Complications in the use of Factor IX Concentrate DE.FIX are rare. Apart from the general complications of hepatitis, products containing concentrations of coagulation factor IX have a well documented reputation for causing diffuse intravascular coagulation or thrombosis at the injection site. Although factor IX concentrate (DE.FIX) has not been implicated in episodes of this nature the reason of freedom from such side-effects is not known and caution in use is advised, especially in circumstances where the recipient may have liver disease.

Heparin
This product does not contain heparin.

Reference
Scottish National Blood Transfusion Service
Protein Fractionation Centre
21 Ellen's Glen Road
Edinburgh
EH17 7QT

P. F. C. 29A Waddie & Co. 2.500/83 Prod. Lic.3473/6008
HEAT TREATED
HUMAN FACTOR IX CONCENTRATE (H.T. DEF.IX)

Description This preparation, which is rich in coagulation factors II, IX and X is recovered from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction by adsorption from plasma volumes requiring up to 25,000 donations per batch.

All plasma used for preparation of factor IX concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the Hepatitis B surface antigen using a radioimmunoassay and the preparation has also been examined for this antigen by more searching techniques applied in at least two laboratories. In addition, product, plasma pools and individual plasma donations are tested for the presence of antibody to HTLV II. The product has been heat-treated at 80°C for 72 hours in the freeze-dried state. This treatment is expected to inactivate viruses associated with the Acquired Immune Deficiency Syndrome (HTLV, LAV, ARV) (2, 3, 4). The effect of this heat-treatment on Hepatitis B, and Hepatitis non A—non B has still to be elucidated and therefore, this product cannot be assumed to be non-infective with regard to the hepatitis viruses.

The reconstituted product contains 300 iu Factor IX, not less than 200 iu Factor II and not less than 200 iu Factor X. Anti-Thrombin Ill is added at a concentration no greater than 5 iu per vial. It contains not more than 25g/l total protein, less than 80 m.mol/l citrate ions and less than 50 m.mol/l phosphate ions.

Storage Factor IX Concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below +35°C but at least 90 per cent of the stated potency should be recoverable after 12 months storage at temperatures between 2°C and 5°C. It should not be stored for prolonged periods in the range of +1°C to -1°C and the accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Indications Human Factor IX Concentrate—H.T. DEFIX is issued for treatment of congenital factor IX deficiency (Haemophilia B).

Resolution From the Dry State If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and addition to the dry powder using a syringe and employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within ten minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done taking care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of three hours following resolution.

Reconstituted Factor IX Concentrate solution should not be stored.

Administration Factor IX Concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/min. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids. It may be diluted using sodium chloride injection BP but should be administered quickly following dilution.

The actual volume of solution for any administration depends on the status of the individual patient and the purpose of treatment. Treatment may require to be repeated at varying intervals to maintain the required concentration of factor IX activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects Apart from the general complications of virus transmission (discussed above) products containing concentrations of coagulation Factor IX have a well documented reputation for causing disseminated intravascular coagulation or thrombosis at the injection site. Unheated FIX (DEFIX) manufactured by the Scottish National Blood Transfusion Service, had a good safety record for products of this type. Laboratory data and evaluation in an animal model both suggest that HT DEFIX is superior in this respect to the unheated product. However, as HT DEFIX is a new product, caution in use is advised, especially in circumstances where the recipient may have liver disease, until complete freedom from such side-effects has been confirmed.

Heparin This product does not contain heparin.

References

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
PROTEIN FRACTIONATION CENTRE
21 ELLEN'S GLEN ROAD
EDINBURGH EH17 7GT
SNBTS COAGULATION FACTOR CONCENTRATES

VIAL LABEL

1. Factor VIII Concentrate (unheated)

![Factor VIII Concentrate Image]

Allow Factor VIII and Water for Injections to warm to 20°-30°C before reconstitution. Mix gently to ensure complete solution. Use as soon as possible within 3 hours. Reconstituted product contains less than 100 IU/ml factor VIII, less than 0.1 mg/ml sodium, and less than 0.01 mg/ml calcium. This preparation is of human origin and cannot be assumed free of hepatitis virus.

2. Factor VIII Concentrate (heated at 68°C)

![Factor VIII Concentrate (heated) Image]

3. Factor IX Concentrate (unheated)

![Factor IX Concentrate Image]

Recipients of Factor IX concentrate should be monitored for antibody development.

HUMAN FACTOR IX CONCENTRATE (DEFIX) (LYOPHILISED) CONTENTS 300 IU FACTOR IX, not less than 200 IU FACTOR IX and not less than 200 IU FACTOR X.

Lot EXPRES
STORE AT 2 - 8°C. POM

RECONSTITUTED WITH 10 ml WATER FOR INJECTION.
Human Antihaemophilic Factor
Factor VIII (Lyophilised)

Scottish National Blood Transfusion Service
Protein Fractionation Centre
Ellen’s Glen Road
Edinburgh EH17 7QT

This package contains:— 10 vials of Factor VIII (Lyophilised)
10 vials of Water for Injections (Ph. Eur.)

When reconstituted according to the instructions on the Factor VIII vial, the product contains:—
not more than 60g/l Total Protein
less than 200m mol/l Sodium ions
less than 50m mol/l Citrate ions
Does not contain preservative.

Both the Factor VIII and Water for Injections must be allowed to warm to 20° to 30°C before reconstitution.
Only gentle mixing should be employed during reconstitution. If a gel forms or insoluble material remains, the preparation should not be used. Use the reconstituted solution as soon as possible and in any case within three hours.

This preparation is of human origin and despite careful screening of donations cannot be assumed to be free of hepatitis virus.

The Factor VIII vials must be stored between 0-5°C. Product Licence 3473/0007
Human Antihaemophilic Factor
Factor VIII (Lyophilised)

This package contains:— 10 vials of Factor VIII (Lyophilised)
10 vials of Water for Injections (Ph. Eur.)

When reconstituted according to the instructions on the Factor VIII vial, the product contains:—
not more than 60g/l Total Protein
less than 200mmol/l Sodium ions
less than 50mmol/l Citrate ions
Does not contain preservative.

Both the Factor VIII and Water for Injections must be allowed to warm to 20° to 30°C before reconstitution.

Only gentle mixing should be employed during reconstitution. If a gel forms or insoluble material remains, the preparation should not be used. Use the reconstituted solution as soon as possible and in any case within three hours.

This preparation is of human origin and despite careful screening of donations cannot be assumed to be free of hepatitis virus.

The Factor VIII vials must be stored between 0-5°C.

Product Licence 3473/0007
2a. Examples of Warnings in Documents

Provided by Alpha Therapeutics
Antihemophilic Factor (Human) Lyophilized

**DESCRIPTION**
Antihemophilic Factor (Human) Prothrombin was added to this product by lysine palmitate of the protein factor and its subsequent purification and concentration by chromatographic means.

**INDICATIONS**

- Antihemophilic Factor (Human) Prothrombin is indicated for the replacement of currently deficient or absent antihemophilic factors for the primary treatment of hemophilia A or acquired Factor VIII deficiency. Antihemophilic Factor (Human) Prothrombin is not indicated for the replacement of currently deficient or absent antihemophilic factors in patients with von Willebrand's disease.

**CONTRAINdicATIONS**

There are no known contraindications to the use of Antihemophilic Factor (Human) Prothrombin.

**WARNINGS**

Vital organs may be irreversibly damaged by products of the human or animal tissue. Therefore, all injectable products should be stored in a cool place, preferably at 2-8°C.

**PRECAUTIONS**

Antihemophilic Factor (Human) Prothrombin should be administered at a rate of 80-120 units/kg body weight per minute intravenously.

**ADVERSE REACTIONS**

Adverse reactions can include urticaria, fever, chills, nausea, vomiting, headache, and hypotension. Some patients develop reactions of a minor nature following the administration of Antihemophilic Factor (Human) Prothrombin.

**DO NOT USE IF**

- The patient develops bronchospasm, and the patient requires additional Antihemophilic Factor (Human) Prothrombin product from a different lot is transfused.

**STORAGE:**

- Antihemophilic Factor (Human) Prothrombin may be stored at temperatures between 2°C and 8°C for two years or at room temperature not exceeding 30°C for 6 months.

**REFERENCES**

DATA SHEET

PROFILATE HEAT-TREATED

Wet Method

Presentation

Antihemophilic Factor (Human), Profilate, Heat-Treated is a stable freeze-dried concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma. The potency (AHF activity) is given on the label of each vial in international units (i.u.), one i.u. being defined as the activity present in 1 ml of fresh pooled normal plasma.

Uses

For the prevention and control of bleeding in patients with moderate or severe Factor VIII deficiency (Classical hemophilia A) or acquired Factor VIII deficiency.

Dosage and Administration

Dosage:

Antihemophilic Factor (Human), Profilate, Heat-Treated is intended for intravenous administration within 3 hours of reconstitution with the diluent supplied. The formulae below provide a guide to dosage calculations:

- Number of i.u. of AHF required
- Body weight in lbs
- Desired increase 
- x 20 x in Factor VIII percentage

Number of i.u. of AHF required in Factor VIII percentage
- Body weight in kgs
- Desired increase
- x 44 x in Factor VIII percentage

Mild to moderate haemorrhages may usually be treated with a single administration sufficient to raise the plasma AHF level to 20 to 30 percent. In the event of more serious haemorrhage the patient's plasma AHF level should be raised to 50 to 70 percent.

Infusions are generally required at twice daily intervals over several days. Surgery in patients with Factor VIII deficiency requires that the AHF level be raised to 50 to 80 percent with the level maintained at or above 30 percent for approximately two weeks post-operatively. For dental extractions, the AHF level should be raised to 50 percent immediately prior to the procedure; further Factor VIII may be given if bleeding recurs.

In patients with severe Factor VIII deficiency who experience frequent haemorrhages, Antihemophilic Factor (Human), Profilate, Heat-Treated is administered prophylactically on a daily or every other day schedule so as to raise the AHF level to approximately 15 percent.

Reconstitution:

Use Aseptic technique:

1. Warm diluent and concentrate bottle to at least room temperature (but not above 37°C).
2. Remove plastic flip-off cap from the diluent bottle.
3. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.
4. Remove all covering from one end of a double-ended needle.
5. Insert this exposed end of the needle through the depression in the centre of the stopper in the bottle of diluent.
6. Remove plastic flip-off cap from the concentrate bottle. Tap bottle gently to dislodge concentrate from sides of bottle.
7. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.
8. Remove plastic cap from the upper end of the double-ended needle now seated in the stopper of the diluent bottle. Hold concentrate bottle in one hand, invert the bottle of diluent in the other hand and push the exposed end of the needle through the depression in the centre of the stopper, making certain that the diluent is always above the bottle of concentrate. There should be enough vacuum in the bottle to draw in all the diluent.
9. Disconnect the two bottles by removing needles from the concentrate bottle stopper. Shake vigorously for ten seconds, then agitate or rotate concentrate bottle until all concentrate is dispersed. Reconstitution requires approximately five to ten minutes. When the reconstitution procedure is strictly followed a few small particles may occasionally remain. The filter spike will retain particles and the labelled potency will not be reduced.

Administration:

By syringe.—Use Aseptic technique

1. Peel cover from filter spike package.
2. Remove protective cover from sterile disposable plastic syringe (not included).
3. Securely install the syringe into exposed inner inlet of filter spike using a slight twisting motion.
4. Remove filter spike from blister-pak cup.
5. Insert tapered spike into reconstituted concentrate bottle perpendicular to stopper. If spike is not held perpendicular it may push stopper into bottle rendering contents unusable.
6. Remove and discard the filter spike from the syringe and attach syringe to an infusion set, expel air from syringe, make venipuncture and administer slowly.
7. If the patient is to receive more than one bottle of concentrate the infusion set will allow this to be done with a single venipuncture.
8. Discard all administration equipment after use.

By infusion set.—Use Aseptic technique

1. Close clamp on administration set.
2. With bottle upright, thrust piercing pin straight through stopper centre. Do not twist or angle.
3. Immediately invert bottle to automatically establish proper fluid level in drip chamber (half full).
4. Attach infusion set, open clamp and allow solution to expel air from tubing needle, then close clamp.
5. Make venipuncture and adjust flow.
6. Discard all administration equipment after use.

Contra-Indications:

There are no known contraindications to the use of Antihemophilic Factor (Human), Profilate, Heat-Treated.
Warnings:
This product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and antibody to human T-lymphotropic virus type III (HTLV-III). However, HTLV-III/LAV virus has been implicated as the agent of AIDS. It is not known if other transmissible agents are involved. Despite the careful selection of donors and a heat-treatment step in the manufacturing process, it is possible that the AIDS causative agent may still be present in and transmitted through this product.

The causal factors of Acquired Immunodeficiency Syndrome (AIDS) have not been fully defined. However, HTLV-III/LAV virus appears to be implicated as the agent of AIDS. It is not known if other transmissible agents are involved. Despite the careful selection of donors and a heat-treatment step in the manufacturing process, it is possible that the AIDS causative agent may still be present in and transmitted through this product.

Precautions:

Antihaemophilic Factor (Human), Profilate, Heat-Treated should not be administered at a rate exceeding 10 ml/minute. More rapid administration may result in vasorotor reactions.

Some patients develop inhibitors to Factor VIII. Rarely, other patients acquire similar inhibitors. The management of patients with inhibitors requires careful monitoring, especially if surgical procedures are indicated. In patients with inhibitors, the response to Antihaemophilic Factor (Human), Profilate, Heat-Treated may be much less than would otherwise be expected and larger doses are often required. Patients with high inhibitor levels may not respond to Antihaemophilic Factor (Human), Profilate, Heat-Treated at all.

Nurses and others who administer this material should exercise appropriate caution in handling because of the risk to exposure to viral hepatitis.

Discard any unused contents. Discard administration equipment after single use. Do not resterilize components.

Adverse Reactions:

May include urticaria, fever, chills, nausea, vomiting, headache, somnolence or lethargy. Some patients develop reactions of a mild nature following the administration of Antihaemophiliic Factor (Human), Profilate, Heat-Treated. Adverse reactions may be on an allergic basis. If a reaction is noted and the patient requires additional Antihaemophilic Factor (Human), Profilate, Heat-Treated, product from a different lot should be administered. Massive doses have rarely resulted in acute haemolytic anaemia, increased bleeding tendency or hyperfibrinogenaemia. Antihaemophilic Factor (Human), Profilate, Heat-Treated does contain blood group isagglutinins and when large and/or frequent doses are required in patients of blood group A, B or AB, the patient should be monitored for signs of intravascular haemolysis and falling haematocrit. Should this condition occur, thus leading to progressive haemolytic anaemia, the administration of serologically compatible type O red blood cells should be considered.

Antihaemophilic Factor (Human), Profilate, Heat-Treated may be stored at temperatures between 2° - 8°C for two years. Do not store components above 31°C. Do not freeze.

The process used in the manufacture of Profilate Heat-Treated includes a step designed to reduce the risk of transmission of Hepatitis, Acquired Immune Deficiency Syndrome (AIDS) and infection by other viruses which involves heating a liquid suspension of the product for 20 hours at 60°C.

The effectiveness of the heat-treatment step was assessed by in-vitro inactivation studies using live viruses added to Antihaemophilic Factor (Human), Profilate, Heat-Treated at all. The units of AHF activity expressed as international Units (iu), are stated on the label of each concentrate bottle.

Further Information

The process used in the manufacture of Profilate Heat-Treated includes a step designed to reduce the risk of transmission of Hepatitis, Acquired Immune Deficiency Syndrome (AIDS) and infection by other viruses which involves heating a liquid suspension of the product for 20 hours at 60°C.

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Discard any unused contents. Discard administration equipment after single use. Do not resterilize components.

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May include urticaria, fever, chills, nausea, vomiting, headache, somnolence or lethargy. Some patients develop reactions of a mild nature following the administration of Antihaemophilic Factor (Human), Profilate, Heat-Treated. Adverse reactions may be on an allergic basis. If a reaction is noted and the patient requires additional Antihaemophilic Factor (Human), Profilate, Heat-Treated, product from a different lot should be administered. Massive doses have rarely resulted in acute haemolytic anaemia, increased bleeding tendency or hyperfibrinogenaemia. Antihaemophilic Factor (Human), Profilate, Heat-Treated does contain blood group isagglutinins and when large and/or frequent doses are required in patients of blood group A, B or AB, the patient should be monitored for signs of intravascular haemolysis and falling haematocrit. Should this condition occur, thus leading to progressive haemolytic anaemia, the administration of serologically compatible type O red blood cells should be considered.

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The effectiveness of the heat-treatment step was assessed by in-vitro inactivation studies using live viruses added to Antihaemophilic Factor (Human), Profilate, Heat-Treated at all. The units of AHF activity expressed as international Units (iu), are stated on the label of each concentrate bottle.
2b. Examples of Warnings in Documents

Provided by Baxter (Hyland/Travenol)
DATA SHEET

ANTITHAEMOPHILIC FACTOR (HUMAN)

HEMOFIL

METHOD FOUR

Presentation

Antithaemophilic Factor (Human), HEMOFIL. Method Four is a sterile, lyophilised preparation of human antithaemophilic factor (Factor VIII, AHF, AHG) in concentrated form. It contains minimal quantities of other proteins and approximately 3% w/v dextrose in the reconstituted material as a solubilising agent. The product also contains a trace amount of heparin, 1.0 unit (0.010 mg) or less per ml of reconstituted material, as a stabiliser.

Uses

The product is intended for use in the therapy of classical haemophilia (haemophilia A). It can also be of significant value in patients (not true haemophiliacs) with acquired Factor VIII inhibitors.

Dosage and Administration

1. Dosage

Each bottle of HEMOFIL is labelled with the number of International Factor VIII Units which it contains, 1 unit being defined as the activity present in 1 ml of average normal pooled human plasma less than 1 hour old (100 % AHF level).

The amount of AHF which a haemophiliac requires for normal haemostasis varies with circumstances and the patient. The following formulae can be used to calculate approximately the expected response from a given dose or the dose required for a given effect:

a) Units required = 
body weight (in kg) x 0.4 x desired 
AHF increase (in % of "normal")

or

b) Expected AHF increase (in % of "normal") =
units administered 
body weight (in kg) x 0.4

The data of Biggs et al would call for a factor of 0.5 instead of 0.4 in the above formulae.

Pharmaceutical Precautions

However, each unit of the plasma has been found to be nonreactive for hepatitis B surface antigen by radioimmunoassay. The concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should, therefore, be used when its expected effect is needed, in spite of the hepatitis risk associated with its use. Special consideration should be given to the use of this concentrate in newborns and infants where higher morbidity and mortality may be associated with hepatitis.

Each lot, after reconstitution as for use, has been found nonreactive for hepatitis B surface antigen using a solid phase radioimmunoassay technique. The significance of a nonreactive test result with concentrated antithaemophilic factor has not been established. Therefore, the product should continue to be considered to carry a risk with respect to hepatitis.

The preparation contains blood group isoagglutinins in amounts which are not clinically significant in the dosage needed to control haemarthroses and other relatively slight bleeding episodes in the absence of inhibitors. However, when larger or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, patients of blood groups A, B and AB should be monitored for signs of intravascular haemolysis and falling haematocrit values. Haemolytic anaemia may be corrected by the administration of compatible group O cells.

Since all solutions containing fibrinogen, as does HEMOFIL, tend to cause the around surfaces of glass syringes to stick, plastic (disposable) syringes are recommended whenever administration by syringe is desired. The administration set and any reconstituted concentrate not immediately injected should be discarded.

HEMOFIL should be stored under ordinary refrigeration (2° to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent bottle may occur. HEMOFIL may be stored at room temperature for time periods up to 4 weeks.
There is some evidence that in haemophilic with severe bleeding, particularly if he has not been recently treated, up to double the calculated initial dose may be needed to produce the desired AHF level, after which the formulae apply.

Although dosage can be estimated by these formulae, it is strongly recommended that, whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained.

2. Administration
It is recommended that the solution be administered within three hours after reconstitution, although when reconstituted as directed, the AHF activity is not diminished by holding the material at 20° to 25°C for as long as 1 hour. The reconstituted material should not be refrigerated as irreversible precipitation of active material may occur.

HEMOFIL can be administered by intravenous drip infusion or intravenous syringe injection and details of these methods and the rate of administration are included in the direction sheet. A high potency HEMOFIL (code KD-060-207) is a special preparation containing at least 34 I.U. per ml of reconstituted material and must be administered at a controlled rate, not exceeding 2 ml per minute.

To avoid precipitation of cold-insoluble globulin containing AHF activity, the solution should not be below room temperature during infusion.

### Contraindications and Cautions

1. Contraindications
There are no known contraindications to the use of this concentrate.

2. Cautions
Identification of the deficiency as one of Factor VIII is imperative before administration of this highly purified Antihaemophilic Factor. No benefit may be expected from this product in treating other deficiencies.

This concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agents of viral hepatitis.

### Legal Category
The statutory provisions of the Medicines Act, 1968 shall apply.

### Package Quantities
HEMOFIL is supplied as a complete package. Each package contains all the necessary equipment for administration of the concentrate plus a suitable volume of Sterile Water for Injection for reconstitution and a comprehensive direction sheet.

HEMOFIL is available in the following sizes and activities:

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Average Activity (I.U.)</th>
<th>Code Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml</td>
<td>250</td>
<td>KD-060-209</td>
</tr>
<tr>
<td>30 ml</td>
<td>750</td>
<td>KD-060-205</td>
</tr>
<tr>
<td>30 ml</td>
<td>1050</td>
<td>KD-060-207</td>
</tr>
</tbody>
</table>

*The minimum activity of the concentrate after reconstitution is 10 International Units per ml. The actual potency, as determined for each lot, is stated in International Units on the label of each vial.*

### Further Information
HEMOFIL is not known to contain clotting factors other than AHF in sufficient quantity to be useful therapeutically.

Other advantages of HEMOFIL are:

1. It is of homologous origin and carries no risk of foreign substance reaction.
2. It supplies higher potency AHF than glycine or cryoprecipitate preparations with relatively smaller amounts of fibrinogen and other protein, furnishing adequate AHF without excessively overloading the circulatory system.
3. Sufficient amounts may be administered to overcome inhibitors, thus eliminating the need for bovine or porcine preparations.
4. Because of predictable effect, therapy may be managed without repeated determination of AHF level when the patient is very young, when veins are poor or when laboratory service is not immediately available.

For more detailed information on Antihaemophilic Factor (Human), HEMOFIL, Method Four refer to product direction sheet.

### Product Licence Number
0116/0011

Great Britain Patent Nos. 1,178,958, 1,372,515 and patent pending

HYLAND DIVISION
TRAVENOL LABORATORIES LTD.,
Thetford, Norfolk, England
April 1977
00-XD-00-040
HEMOFIL® AHF Products

For Use in Treatment of Acquired Factor VIII Inhibitors.

The concentrate is not known to contain clotting factors other than AHF in sufficient quantity to be useful therapeutically. The concentrate can be of significant value in patients (not true hemophiliacs) with acquired Factor VIII inhibitors. For example, prompt clinical response was obtained with a similar preparation in a 54 year old female with renal hemorrhage. Prior to infusion, 1 ml of her plasma neutralized 15 units of AHF. After intravenous drip infusion of 35,000 units of AHF in 90 minutes, circulating inhibitors were overcome and hemostasis was obtained. A month later, her inhibitor level dropped from 15 units to 4 units, and her partial thromboplastin time shortened from 140 seconds to 88 seconds. In such other uses, the dosage of the concentrate should be controlled by frequent laboratory determinations of circulating AHF.

Cautions

Identification of the deficiency as one of Factor VIII is imperative before administration of this highly purified Antihemophilic Factor. No benefit may be expected from this product in treating other deficiencies.

This concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agents of viral hepatitis. However, each unit of the plasma has been found to be nonreactive for hepatitis B surface antigen (HbsAg) by counterelectrophoresis or radioimmunoassay. The concentrate has not been subjected to the treatment known to diminish the risk of transmission of hepatitis since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should therefore be used when its expected effect is needed in spite of the unknown hepatitis risk associated with its use. Special consideration should be given to the use of this concentrate in newborns and infants where a higher morbidity and mortality may be associated with hepatitis.

No reactions have been reported similar to those described in individuals receiving multiple transfusions of plasma. However, the physician should be prepared to treat such a reaction if it should occur.

This preparation contains blood group isoagglutinins in amounts which are not clinically significant in the dosage needed to control hemarthroses and other relatively slight bleeding episodes in the absence of inhibitors. However, when larger or frequently repeated doses are needed, as when inhibitors are present or when pre and post surgical care is involved, patients of blood groups A, B, and AB should be monitored for signs of intravascular hemolysis and failing hematocrit values. The only reported case showing this phenomenon is that of a young 140 pound adult surgical patient of blood group A who received 40,000 AHF units over 40 days without ill effects, then in the following 9 days received 57,000 AHF units. During the latter 9 days, he exhibited progressive hemolysis, falling hematocrit, positive Coombs test, and circulating anti-A agglutinin. His anemia was corrected by the administration of compatible group O cells. The reported anti-A content of one lot of Antihemophilic Factor (Human) which he received is not typical of current production.

Contraindications

There are no known contraindications to the use of this concentrate.

Three amino acid (glycine) content of the concentrate has been reduced to less than 0.038 g per ml of reconstituted product. It is theoretically possible that very intensive therapy with this concentrate in a patient with severe liver or kidney damage could overload the "detoxification" mechanism, but no clinical or laboratory evidence of this has been seen.

Reconstitution

It is recommended that the solution be administered within three hours after reconstitution. The reconstituted concentrate should immediately be injected or placed in a constant temperature water bath at 8°C, 35° to 46°F. Freezing should be avoided as breakage of the diluent bottle might occur.

NOTE: Directions for use are provided with each product.

Storage

HEMOFIL Antihemophilic Factor (Human), Method Four, Direct Dial, should be stored under ordinary refrigeration (2 to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent bottle might occur.

In Alaska, California, Canada, Hawaii call (714) 540-5000
2c. Examples of Warnings in Documents

Provided by Cutter (Miles/Bayer)
Antihemophilic Factor (Human)

Antihemophilic Factor (Human) is a plasma protein derived from human plasma that corrects the coagulation defect of patients with classical hemophilia B, hemophilia A, and von Willebrand's disease. It is used for the treatment of hemorrhage in these conditions and is also used in surgery on hemophiliacs.

METHOD

Antihemophilic Factor (Human) is intended for intravenous administration. The dose of the concentrate must be calculated based on the patient's body weight and the specific indications for which it is being used. The dose is calculated as follows:

- For hemophilia B: 50 units/kg body weight
- For hemophilia A: 30 units/kg body weight
- For von Willebrand's disease: 50 units/kg body weight

The dose is administered over 1 to 2 hours. The solution must be diluted in a compatible intravenous solution before administration. It is not recommended to use other diluents such as lactated Ringer's solution or albumin.

ADVERSE REACTIONS

Adverse reactions are uncommon but may include:

- Vascular occlusion
- Allergic reactions
- Severe anaphylactic reactions

The solution should be inspected for particulate matter and color change before administration. If the solution is cloudy or contains particulate matter, it should not be administered.

REFERENCES

KOATE- HT
Dried Factor VIII Fraction Heat-treated

PRESENTATION
Koate-HT is a stable purified dried concentrate of human Factor VIII (Antihamaophilic Factor) prepared from the cold insoluble fraction of pooled fresh-frozen plasma. When reconstituted with Water for Injection, it contains 25-40 times as much Factor VIII as an equal volume of fresh plasma. Koate-HT has been heat-treated at 68°C for 72-77 hours.

Koate-HT is a white, sterile, lyophilised powder presented in vials containing approximately 250, 500, 1,000 or 1,500 International Units of Factor VIII. One International Unit (IU) is defined by the use of the World Health Organisation Standard for Blood coagulation Factor VIII, human.

A vial containing a suitable volume of Sterile Water for Injection, a sterile filter needle and a sterile double-ended transfer needle are also provided.

USES
For the treatment of classical haemophilia (haemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koate-HT provides a means of temporarily replacing missing clotting factor in order to correct or prevent bleeding episodes or in order to facilitate emergency and elective surgery on haemophiliacs. Dried Factor VIII Fraction is not effective in the treatment of Von Willebrand’s disease.

DOSAGE & ADMINISTRATION
Dosage
Each vial of Koate-HT has the Factor VIII activity in IU’s stated on the label.

The following formulae provide a guide for dosage calculations:

Expected Factor VIII increase (in % of normal) =

\[
\frac{\text{IU administered} \times 2.0}{\text{body weight (in kg)}}
\]

It should be emphasised, however, that all efforts should be made to follow the course of therapy with Factor VIII level assay. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained.

Mild to moderate haemorrhages may be treated with sufficient Koate-HT to raise the plasma Factor VIII level to 20-30% of normal. If the haemorrhage is moderate or if minor surgery is contemplated, a level of 30-50% of normal should be achieved. Severe haemorrhage may require levels of 80-100% of normal in order to achieve haemostasis. Single doses may suffice for treatment of mild haemorrhage, but more severe illness may require multiple daily doses to achieve desired levels.

It should be emphasised that the above dosage recommendations are presented for guidance. The dosage required for normalising haemostasis must be determined according to the needs of the individual patient.

Thus, factors to be considered include the weight of the patient, the severity of the deficiency, the severity of haemorrhage, the presence of inhibitors and the Factor VIII level desired. All efforts should be made to follow the course of therapy with Factor VIII level assays.

The clinical effect of Factor VIII on the patient is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koate-HT than would be estimated in order to attain satisfactory clinical results. If the Factor VIII level fails to attain that expected, or if bleeding is not controlled after adequate calculated dosage, the presence of Factor VIII inhibitor should be suspected. Its presence should be confirmed and the inhibitor level quantitated by appropriate laboratory procedure. When an inhibitor is present, the dosage requirement for Factor VIII is extremely variable and the dosage can be determined only by the clinical response.

Reconstitution and Administration
1. Warm the unopened diluent (Sterile Water for Injection USP) and Factor VIII concentrate to room temperature but not higher than 37°C, 99°F.

2. Remove the plastic flip-top caps from both bottles and cleanse the rubber stoppers with a suitable antiseptic immediately before each piercing.

3. Remove the protective cover from one end of the double-ended transfer needle.

4. Remove the protective plastic from the other end of the needle.

5. The vacuum will transfer the diluent into the concentrate bottle. Avoid excessive foaming. Do not shake the concentrate bottle at any time. If the vacuum is not present, the diluent will not flow and that bottle should not be used.

6. After removing the diluent bottle and needle, very gently rotate the Koate-HT bottle in order to dissolve the concentrate.

7. After the concentrate is completely dissolved, withdraw the Koate-HT solution into the syringe through the filter needle which is supplied in the package. Replace the filter needle with an appropriate sterile injection needle, e.g., 21 gauge x 1 inch, and inject intravenously.

8. If the same patient is to receive more than one bottle of Koate-HT the contents of two bottles may be drawn into the syringe through filter needles before attaching the injection needle.

Contraindications
There are no specific contraindications to the use of Dried Factor VIII Fraction. (Please read Uses section carefully before use).
Precautions
1. Koate-HT is intended for the treatment of bleeding disorders arising from a deficiency of Factor VIII. This deficiency should be proven prior to administering Koate-HT, since no benefit may be expected from its use in treating other causes of haemorrhage.
2. After reconstitution, administer as promptly as possible and within 3 hours. Do not refrigerate after reconstitution.
   NOTE: Koate-HT is fully stable without potency loss for at least 24 hours at room temperature after reconstitution. The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koate-HT, in the unopened vial, is sterile.
3. Administer only by the intravenous route.
4. A filter needle should always be used for transfer to syringe prior to administering.
5. Koate-HT contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required in patients of blood groups A, B or AB, the possibility of the onset of intravascular haemolysis should be considered.
6. Administration equipment and any reconstituted Koate-HT not used should be discarded.

Warnings
1. Allergic reactions including chills, fever and hypersensitivity reactions, may result from the administration of Factor VIII preparations.
2. When large or frequently repeated doses are required in patients of blood groups A, B or AB, there is a possibility of intravascular haemolysis. Should this condition occur leading to progressive anaemia, administration of serologically compatible type O packed red blood cells should be considered. Also, the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.
3. Massive doses of Factor VIII preparations may result in hyperfibrinogenaemia.
4. Koate-HT concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate-HT should be weighed against the medical consequence of withholding it, particularly in persons who have had few previous transfusions of blood or blood products, Koate-HT should be stored under refrigeration (2 to 8°C). Storage of lyophilised powder at room temperature (up to 25°C) for three months, such as in home treatment situations, may be carried out without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur.

LEGAL
CATEGORY
PACKAGE
QUANTITIES
FURTHER
INFORMATION

PRODUCE
PL 0055/0107
Licence No.
Cutter Division,
Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
Berkshire,
SL2 4LY

NAME AND
ADDRESS
OF LICENCEE

*Trade mark of Miles Laboratories Inc., U.S.A.

February 1985
FACTOR X COMPLEX (HUMAN) (FACTORS VII, IX, AND X) Konyn

SEE SECTIONS ENTITLED "INDICATIONS" AND "WARNING" FOR DESCRIPTION OF HEPATITIS RISK.

DESCRIPTION FACTOR X COMPLEX MANUFACTURED BY:

1. A compilation of studies demonstrating the therapeutic efficiency of each of the components of the factor complex, including administration of factor VII, IX, and X in patients with purpura fulminans,

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2d. Examples of Warnings in Documents

Provided by Immuno Ltd.
Bleeding from skin, nose and oral mucous membrane:
Initial dose should be 10 i.u./kg. at intervals of 6 to 12 hours.

Haemarthrosis:
The initial dose should be approximately 10 i.u./kg. and the maintenance dose 5 to 10 i.u. per kg. at intervals of 6 to 12 hours. Combined with immobilisation of the affected joint for several days, the treatment should be sufficient to restore function.

Bruising:
In most cases a single dose of 10 i.u./kg is sufficient. For widespread bruising, repeated administration of 5 to 10 i.u./kg. at intervals of 6 to 12 hours may be required.

Heavy bleeding into muscles:
Immediate treatment is required to prevent permanent deformity and loss of function, and initial immobilisation of the affected area is important. An initial dose of 15 to 20 i.u./kg. should be given, the maintenance dose to be 10 i.u./kg. at intervals of 6 hours from the first to the second day and at intervals of 12 hours from the third to the fifth day.

Haematuria:
The initial dose should be 15 to 20 i.u./kg., and the maintenance dose 10 i.u./kg. at intervals of 12 hours.

Major surgery on haemophilic patients:
The initial dose should be at least 25 to 50 i.u./kg., and the maintenance dose 20 to 40 i.u./kg. at intervals of 4 hours from the first to the fourth day, of 8 hours from the fifth to the eighth day, and of 12 hours until all wounds are healed.
The effect of treatment must be checked daily. Factor VIII activity should not be allowed to fall below 50% of the normal 100% average value. It is important that treatment be continued until all wounds have healed completely, as the risk of haemorrhage persists until then.
In addition to monitoring Factor VIII activity, tests for the development of Factor VIII inhibitors should also be made.

Dental extractions:
The required dosage depends on the number and type of teeth to be extracted, and on the severity of the haemophilia. If one or two teeth are to be extracted from a patient with severe haemophilia, an initial
dose of 10 to 20 i.u./kg. should be given. Maintenance treatment with this dosage at intervals of 6 hours from the first to the third day, and 8 hours from the fourth to the eighth day after extraction, should be given. If more than two teeth are to be extracted from patients with severe haemophilia a minimum initial dose of 20 to 30 i.u./kg. should be given, and a maintenance dose of 10 to 20 i.u./kg. at intervals of 6 hours from the first to the third day, and of 8 hours for twelve more days. The plasma concentration of Factor VIII should not be allowed to fall below 10% of the normal 100% average value.

Factor VIII assays should be used to monitor the effectiveness of treatment, as partial thromboplastin time gives a less accurate value when large quantities of Kryobulin are being used.

Solutions of Kryobulin must be administered intravenously, at a rate not exceeding 10 ml. in 3 minutes.

Although the danger of volume overload is small with Kryobulin, during major surgery monitoring of the patient's central venous pressure and blood pressure, and serial chest X-rays, may be advisable. In disseminated intravascular coagulation associated with low Factor VIII levels Heparin should be given to interrupt intravascular coagulation before therapy with Kryobulin is started.

A low incidence of adverse reactions is experienced with Kryobulin, but the following may occur:

1. Allergic reactions
   All forms of allergic reaction from mild and transient urticaria to severe anaphylactic shock are possible when human plasma derivatives are administered. If such reactions occur, treatment with Kryobulin must be interrupted at once. Allergic reactions should be controlled with antihistamines and corticosteroids and routine treatment given for anaphylactic shock.
   Monitoring of pulse rate and blood pressure is essential. If the pulse rate increases and/or blood pressure falls transfusion of 5% Dextrose should be started.

2. Hepatitis
   Despite the precautions taken in the selection and testing of donors and donations, the risk of transmitting hepatitis cannot be entirely excluded.

3. Factor VIII Inhibitors
   The appearance of a circulating Factor VIII inhibitor is possible. Its appearance cannot be predicted as it does not relate to the amount of Kryobulin administered, nor to the frequency of administration. As far as is known neither corticosteroids nor immunosuppressive agents significantly influence the formation of inhibitors.

Kryobulin must be stored between 2° and 6°C, and protected from light. It then has a shelf-life of two years. When stored between +20°C and +30°C it has a life of six months.

legal category: P.O.M.

package quantity: Kryobulin Home Treatment Pack
   Each pack contains:
   1 rubber capped vial containing 250 or 500 i.u. Dried Human Antihaemophilic Fraction BP
   1 rubber capped vial containing Water for Injections BP
   This pack also contains a syringe 1/V needles, winged adaptor needle and filter needle.

Kryobulin Hospital Pack
   Each pack contains:
   1 rubber capped vial containing 1,000 i.u. Dried Human Antihaemophilic Fraction BP
   1 rubber capped vial containing Water for Injections BP
   The pack also contains a filter needle.
   All three presentations of Kryobulin are available in red packs where the product is obtained from European plasma and blue packs where the product is obtained from American plasma.

Further information:
Kryobulin is especially suitable for Home Treatment. Packs contain all requirements and can be stored in a domestic refrigerator for two years and for up to six months at room temperatures not exceeding 30°C.

Product Licence Number: 0215/0003

Product Licence Holder: Immuno Limited, Arctic House, Rye Lane, Dunton Green, Nr. Sevenoaks, Kent TN14 5HB Tel. No: Sevenoaks (0732) 50342 & 58101 Telex No: 95413

date of preparation: February 1979

Kryobulin is a registered trade-mark.
name of product: PROTHROMPLEX™ Partial Prothrombin Complex (Human). Prothromplex contains coagulation Factors II, IX & X and is indicated for the treatment of Factor IX deficiency (Haemophilia B)

presentation: Prothromplex is a white, amorphous freeze-dried powder or friable solid without any characteristic odour. It is packed in rubber-capped vials containing 200 units or 500 units each of Factors II, IX & X. It is prepared from the plasma of suitable human donors whose transaminase levels are constantly checked and whose donations are shown by RIA to be free from HBsAg. Pooled plasma and the final product are also tested by RIA for freedom from HBsAg. Prothromplex is also tested to discount the likelihood of causing disseminated intravascular coagulation.

uses: Treatment of cases of Factor IX deficiency (Haemophilia B)

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), however the most reliable results are obtained by quantitative activity assays of Factor IX.

Immediately before use Prothromplex must be dissolved in 10 ml of the solvent provided.

After sterilising the cap of the solvent bottle remove 10 ml using the disposable syringe and one of the needles provided. Next sterilise the cap of the Prothromplex bottle and introduce the solvent using the second disposable needle. Reconstitute by gently shaking to and fro, thus avoiding frothing. Withdraw the reconstituted Prothromplex, then remove the syringe from the needle and attach the third disposable needle.

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

Prothromplex is now ready for slow intravenous injection taking about ten minutes.

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 Factor IX deficiency is given in the guide below.

Dosage guide for the treatment of severe and semi-severe cases of Factor IX deficiency:

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

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

<table>
<thead>
<tr>
<th>CLINICAL Manifestation</th>
<th>Therapeutically wanted minimum Factor IX level</th>
<th>Initial dose in units Factor IX per kg bodyweight</th>
<th>Maintenance dose at intervals of 8 to 12 (24) hours in units Factor IX per kg bodyweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>surface bleedings of the skin and mucosae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>superficial or deep haematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haemarthoses</td>
<td>5 - 10%</td>
<td>15 U</td>
<td>7 - 15 U</td>
</tr>
<tr>
<td>slight bleedings following injuries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uncomplicated dental extractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe muscle haematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate bleedings following injuries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gastric and intestinal haemorrhages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bone fractures</td>
<td>15 - 30%</td>
<td>20 - 30 U</td>
<td>15 - 30 U</td>
</tr>
<tr>
<td>cerebral bleedings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complicated dental extractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minor surgery</td>
<td>more than 50%</td>
<td>75 U</td>
<td>50 - 75 U</td>
</tr>
<tr>
<td>major surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaeamophilic Fraction.
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 initial short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of Factor IX, which is approx. 12-30 hours, a successful result will be achieved by repeated administration of Prothromplex at intervals of 6-12 hours. To assure absolute control of treatment, determination of the PTT should be made and, where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free post-operative 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 circulating coagulation Factor IX is achieved. The danger of volume or protein overloading of the patient is avoided even with the administration of high dosage.

contra-indications, warnings, etc. : With patients suffering from disseminated intravascular coagulation, (DIC), Prothromplex should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

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 shoc 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 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 in the checking of donors, donations and the final product, the transmission of 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 the administration. As far as is known neither corticosteroids nor immunosuppressive agents significantly influence the formation of inhibitors.

pharmaceutical precautions : Prothromplex has a shelf-life of one and a half years when stored between +2^\circ C and +6^\circ C, protected from light.

legal category : P.O.M.

package quantity : 200 units or 500 units of Factors II, IX and X in each container.
   1 rubber-capped vial containing lyophilised Prothromplex.
   1 rubber-capped vial containing 10 ml Water for Injections B.P.
   1 10 ml disposable syringe.
   3 disposable needles.

further information : Prothromplex can be stored in a domestic refrigerator, and can therefore be kept available for home treatment.
Prothromplex can be given in small volume injections, and is therefore suitable for home treatment.
Prothromplex can be moved in insulated containers to a refrigerator at some other location, giving a patient a greater degree of mobility.

product licence number, name and address : Product Licence Number: 0215/006

Product Licence Holder:
Immuco Limited,
Arctic House, Rye Lane, Dunton Green,
Nr Sevenoaks, Kent TN14 5HB
Tel. No: Sevenoaks (0732) 58101 & 50342
Telex No. 95413

date of preparation : May 1979

Prothromplex is a trade mark