NHS
National
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Scotland

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

PENROSE INQUIRY

RESPONSE to PENROSE INQUIRY REQUEST No 8.5
Hepatitis Risk Warnings

RELEASE AUTHORISATION

Author: _____ Date 10/6/10

NMSD: _____ Date 9 Jun 2010

NHS
National
Services
Scotland

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

PENROSE INQUIRY

HEPATITIS RISK WARNINGS

Penrose Inquiry – NHS Central Legal Office – Outstanding Matter No. 8.4

Request for Evidence of Warnings of Risk of Hepatitis Issued with Certain Factor Concentrates.

"I would also like to see evidence of the warnings of risk of hepatitis issued with the coagulation factors referred to by the SNBTS at para 1.4 on page 8 of the Events paper

(i) evidence of the warnings of risk of hepatitis issued with coagulation factor concentrates prepared by the SNBTS
(ii) evidence of the hepatitis warnings issued by Hyland, Cutter, Immuno and Alpha Therapeutics as shown in product literature and information leaflets

I assume that SNBTS will have that evidence in relation to its own products. I am not clear to what extent SNBTS will have the information in relation to commercial products but I assume that it should be held by the Haemophilia Centres that purchased and used such commercial products. Perhaps you could confirm."

Response

A risk of hepatitis transmission by coagulation factor concentrates was well established by the early 1970s. Warnings of this risk were provided by manufacturers, including the SNBTS who provided warnings of risk printed on the packaging and the vial label as well as in an information leaflet supplied with the product.

As coagulation factor concentrates are prescription-only products, manufacturers are not allowed to communicate with patients directly and communication of warnings to individual patients is the responsibility of the prescribing doctor.

Copies of the documents requested by the Penrose Inquiry were provided by the SNBTS to the Inquiry held by Lord Archer of Sandwell and are published on the SNBTS website; www.scotblood.co.uk/publications. A copy of this document is appended and the contents are summarized below.

1. **Warnings Concerning Coagulation Factor Concentrates Prepared by the SNBTS**

Warnings concerning coagulation factor concentrates prepared by the SNBTS are given in pages 6-21 of the document supplied to Lord Archer. Specifically:

1.1. Product Licence Applications: General Information.

Page 7 is taken from the first (March 1978) SNBTS Product Licence Application for Factor VIII concentrate; in section 2.6, headed *"Contra-indications, Precautions and Warnings"* the SNBTS advises that the *"Product may carry the risk of transmitting serum hepatitis"*. The same warning was given in the first (October 1978) Product Licence Application for the SNBTS Factor IX concentrate and is shown on page 11.

1.2. Product Licence Applications: Package Inserts

The text of package inserts must be included in applications for Product Licences and are approved by the Committee on Safety of Medicines (CSM) when a Product Licence is granted. The wording proposed by the SNBTS in its first Product Licence Applications is shown on pages 8-9 for Factor VIII concentrate and on pages 13-14 for Factor IX concentrate. The warnings given for both products were the same, namely:

> ***Description*** (2nd paragraph) - *"Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis."*
>
> ***Side Effects*** (last paragraph) – "*Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis .....*"

1.3. Package Inserts

The wording of the first package inserts provided by the SNBTS was identical to that given in the Product Licence Application. These package inserts (leaflets) were enclosed with each carton of product from the time that the Product Licence was granted.

Actual package inserts are shown for unheated factor VIII concentrate (page 15), heat treated Factor VIII concentrate, dated 1985 (page 16), factor IX concentrate, dated 1983 (page 17) and heat treated factor IX concentrate, dated 1986 (page 18).

1.4. Vial Labels

The label attached to each vial of SNBTS product contained warnings. Examples of these labels are shown on page 19, with the following wording:

> "*This preparation is of human origin and cannot be assumed free of hepatitis virus.*" (unheated Factor VIII concentrate), label dated 1984
>
> "*The freeze dried product has been heat treated but cannot be assumed to be non-infective.*" (heat treated Factor VIII concentrate), label dated 1985
>
> "*This preparation is of human origin and cannot be assumed free of hepatitis virus.*" (unheated Factor IX concentrate), label dated 1984

1.5. Product Packaging

The outer packaging in which vials of coagulation factor concentrates were distributed also contained warnings. An example of this is shown on pages 20 and 21 where all four sides of the carton containing vials of unheated factor VIII concentrate are shown. Two sides of the carton contain the warning:

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

2. **Warnings Issued With Commercial Products**

The SNBTS holds some literature distributed by commercial companies. The following examples are contained in the document provided to Lord Archer.

2.1. Alpha Therapeutics

Warnings provided by Alpha Therapeutics can be seen on:

- page 23, general leaflet, dated 1979(unheated Factor VIII concentrate),
- pages 24-25, UK leaflet, dated 1986 (heat treated Factor VIII concentrate).

2.2. Baxter (Hyland/Travenol)

Warnings provided by Baxter can be seen on:

- pages 27-28, UK leaflet, dated 1977 (unheated Factor VIII concentrate),
- page 29, general leaflet, dated 1975 (unheated Factor VIII concentrate).

2.3. Cutter (Miles/Bayer)

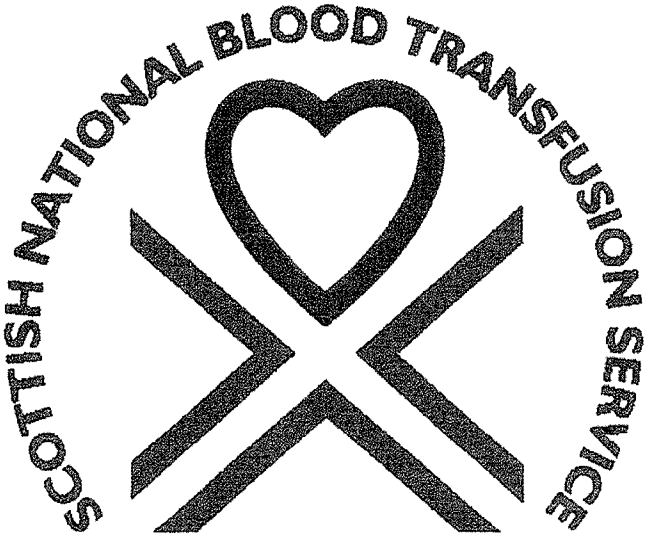
Warnings provided by Cutter can be seen on:

- page 31, general leaflet, dated 1978 (unheated Factor VIII concentrate),
- pages 32-33, UK leaflet, dated 1985 (heat treated Factor VIII concentrate),
- page 34, general leaflet, dated 1978 (unheated Factor IX concentrate).

2.4. Immuno Ltd.

Warnings provided by Immuno can be seen on:

- pages 36-37, UK leaflet, dated 1979 (unheated Factor VIII concentrate)
- pages 38-39, UK leaflet, dated 1979(unheated Factor IX concentrate).



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 (Koāte) – USA leaflet (1978)
Factor VIII concentrate, dry-heated at 68°C (Koāte-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

MEDICINES ACT 1968 and 1971 - APPLICATION FOR PRODUCT LICENCE — PLA 201 Page 1

1.1. Name of Product: Human Antihaemophilic Factor: Factor VIII (Lyophilised)

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.
[redacted]

1.5 Activities for which licence is required:
[redacted]
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK.
[redacted]

1.6. Applicants own reference no: PLA 004/77

1.7. Details of earlier applications: None

1.8. To cover [redacted] supply of the product manufactured before the grant of the licence: YES/[redacted]

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

1.10. Number of pages of supplementary information:

1.11. I/We 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 as Uses, and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the licensing authority.

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.

Date 30th March 1978

Signature [signature] for the Management Committee.

State capacity in which signed.

For licensing authority use

Product Particulars

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 **Uses:** 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

Applicants reference number (as on page 1) 004/77

Applicants signature.....

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°C. Maintenance of potency is best achieved at temperatures below -35°C but at least 90% 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 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 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 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 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

1. Newman, J., Johnson, A.J., Karpatkin, M.H. and Puszkin (1971) British Journal of Haematology 21: 1-20.

2. James, H.L. and Wickerhauser, M. (1972) Vox Sanguinis 23: 402-412

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

MEDICINES ACT 1968 and 1971 - APPLICATION FOR PRODUCT LICENCE

PLA 201
Page 1

1.1. Name of Product: 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.

[redacted]

1.5. Activities for which licence is required:

[redacted]
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK.
[redacted]

1.6. Applicants own 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: YES/NO

1.9. Scientific Evidence:

(i)	Chemistry and Pharmacy	Pages
(ii)	Experimental and Biological Studies	Pages
(iii)	Clinical Trials	Pages

1.10. Number of pages of supplementary information:

1.11. I/We 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 as Page, 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.

Date. 30th October 1978

Signature. G. R. S. Watt
State capacity in which signed. for the Committee

For licensing authority use

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 resolution 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 Uses: 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 retail sale or supply: 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

Applicants reference number (as on page 1) 008/78

Applicants signature ..... 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[1].

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

1. Middleton, S.M., Bennet, I.H. and Smith, J.K. (1973) Vox Sang. 24 : 441-456.

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

HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII CONCENTRATE

(LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared 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 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 60gl⁻¹ 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 below −35°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 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 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 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

1. Newman, J., Johnson, A. J., Karpatkin, M. H. and Puszkin (1971) British Journal of Haematology 21:1-20.
2. James, H. L. and Wickerhauser, M. (1972) Vox Sanguinis 23:402-412.

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

P.F.C.358 Waddie & Co. Prod.Lic.3473/0007

HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII CONCENTRATE – HT

(LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared 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 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.

The product has been heat treated at 68°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 – 35°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 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 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

1. Newman, J., Johnson, A.J., Karpatkin, M.H. and Puszkin (1971) British Journal of Haematology 21:1-20.
2. James, H.L. and Wickerhauser, M. (1972) Vox Sanguinis 23:402-412.
3. MMWR Vol 33 No 42 1984 Page 589-591.

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 indated 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[1].

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 iu Factor IX, not less than 200 iu Factor II and not less than 200 iu Factor X. It contains not more than 20g/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 and 5°C. It should not be stored for prolonged periods in the range of +1° to—1°C and the accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Indications

Human Factor IX Concentrate—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 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 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 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 DEFIX 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 (DEFIX) 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

1. Middleton, S. M., Bennet, I. H. and Smith, J. K. (1973) Vox Sang. *24*:441-456.

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P.F.C. 29A Waddie & Co. 2,500/83 Prod. Lic.3473/0008

HEAT TREATED

HUMAN FACTOR IX CONCENTRATE (H.T. 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 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 HTLVIII. 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 (HTLVIII, 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 III 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 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/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

1. Middleton, S. M., Bennet, I.H. and Smith, J. K. (1973) Vox Sang. 24:441-456.
2. MMWR (1984):33:589-591.
3. Levy, J. A., Mitra, G. A., Wong, M. F., Mozen, M. M., (1985):Lancet 1:1456-1457.
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SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
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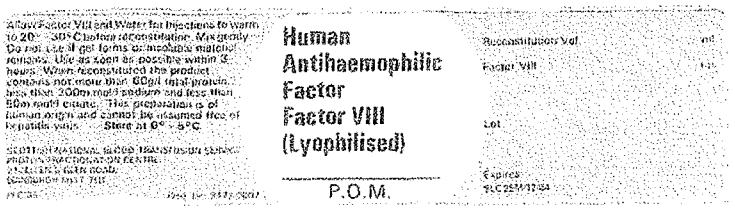
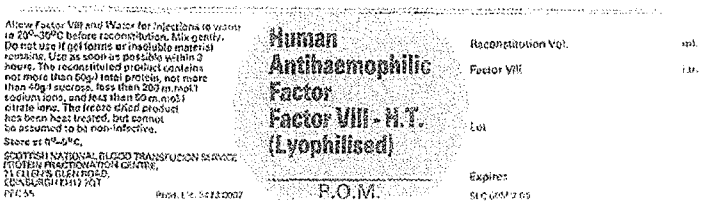
SNBTS COAGULATION FACTOR CONCENTRATES

VIAL LABEL

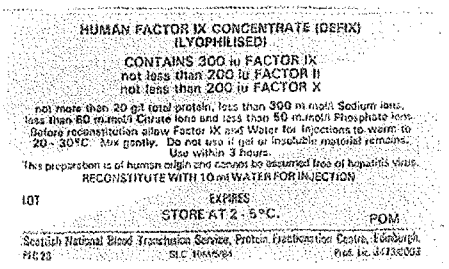
1. Factor VIII Concentrate (unheated)



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



3. Factor IX Concentrate (unheated)



PEN.012.0310

Human Antihaemophilic Factor
Factor VIII (Lyophilised)

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

Human Antihaemophilic Factor
Factor VIII (Lyophilised)

POM

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)

POM

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

2a. Examples of Warnings in Documents Provided by Alpha Therapeutics

PRESCRIBING INFORMATION

Antihemophilic Factor (Human)

Lyophilized

Profilate®

DESCRIPTION

Antihemophilic Factor (Human) Profilate[®] is a stable freeze dried concentrate of Factor VIII (AHF; AHG) prepared from pooled plasma by cryoprecipitation of the active factor and its subsequent purification and concentration by chemical means.

This product is prepared from units of human plasma which have been tested and found nonreactive for hepatitis B surface antigen (HBsAg) by FDA required test. However, presently available methods are not sensitive enough to detect all units of potentially infectious plasma, and the risk of transmitting hepatitis is still present.

ACTIONS

Antihemophilic Factor (Factor VIII) is a constituent of normal plasma required for clotting. The administration of Antihemophilic Factor (Human) Profilate[®] temporarily increases the plasma levels of this clotting factor, thus minimizing the hazards of hemorrhage. Following administration, the half-disappearance time of Factor VIII from the plasma is ordinarily about eight hours.

INDICATIONS

Antihemophilic Factor (Human) Profilate[®] is indicated solely for the prevention and control of bleeding in patients with moderate or severe Factor VIII deficiency due to hemophilia A, or acquired Factor VIII deficiency. Antihemophilic Factor (Human) is not indicated in the management of bleeding in patients with von Willebrand's disease.

CONTRAINDICATIONS

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

WARNINGS

Viral hepatitis may be transmitted by this product. Patients with mild deficiencies, who consequently have not received multiple transfusions of blood or blood products, are at greatest risk.[12,61] In this situation, the benefits of Antihemophilic Factor (Human) administration must be carefully weighted against the risk of viral hepatitis; single donor products should be preferentially utilized whenever feasible.

PRECAUTIONS

Antihemophilic Factor (Human) should not be administered at a rate exceeding 10 ml/minute. Rapid administration may result in vasomotor reactions.

Approximately five to eight percent of hemophilia A 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 Antihemophilic Factor (Human) may be much less than would otherwise be expected and larger doses are often required. Patients with high inhibitor levels may not respond to Antihemophilic Factor (Human) at all.[62,63,64,65]

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

ADVERSE REACTIONS

Adverse reactions can include urticaria, fever, chills, nausea, vomiting, headache, somnolence or lethargy. Some patients develop reactions of a mild nature following the administration of Antihemophilic Factor (Human).[66] Adverse reactions may be on an allergic basis. If a reaction is noted and the patient requires additional Antihemophilic Factor (Human), product from a different lot should be administered.

Massive doses have rarely resulted in acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.[2,4,67]

Profilate[®] does not contain blood group isoagglutinins 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 hemolysis and falling hematocrit. Should this condition occur, thus leading to progressive hemolytic anemia, the administration of serologically compatible type O red blood cells should be considered.

DOSAGE AND ADMINISTRATION

Antihemophilic Factor (Human) Profilate[®] must be administered intravenously within three hours following reconstitution with the diluent supplied. Profilate[®] may be administered either by injection (plastic syringe only) or infusion.

Each bottle of Profilate[®] is labeled with the total units of AHF contained therein. One unit is defined as the activity of one ml of average normal plasma. The following formula provides a guide for dosage calculations:

Number of AHF units required	=	Body weight in lbs	x 20 x	Desired increase in Factor VIII percentage

Example: 110 lbs x 20 x 0.30 = 660 AHF units

or

Number of AHF units required	=	Body weight in kg	x 44 x	Desired increase in Factor VIII percentage

Example: 50 kg x 44 x 0.30 = 660 AHF units

Mild to moderate hemorrhages 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 hemorrhage the patient's plasma AHF level should be raised to 30 to 50 percent; infusions are generally required at twice daily intervals over several days.[68]

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 postoperatively. 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.[1,68]

In patients with severe Factor VIII deficiency who experience frequent hemorrhages, Antihemophilic Factor (Human) Profilate[®] is administered prophylactically on a daily or every other day schedule so as to raise the AHF level to approximately 15 percent.[69]

RECONSTITUTION

USE ASEPTIC TECHNIQUE

1. Warm diluent and concentrate bottles 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 any excess cleaning agent in indentation on stopper.)
4. Remove an covering from one end of a double ended needle. Insert this exposed end of the needle through the depression in center of the stopper in the bottle of diluent.
5. Remove plastic flip-off cap from the concentrate bottle. Tap bottle gently to dislodge concentrate from sides of bottle.
6. Swab the exposed rubber surface with alcohol. (Do not leave any excess cleaning agent in indentation on stopper.)
7. 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 center 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.
8. Disconnect the two bottles by removing needle from concentrate bottle stopper. Shake vigorously for ten seconds, then agitate or rotate concentrate bottle until all concentrate is dissolved. Reconstitution requires approximately five to ten minutes. When the reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Profilate[®] filter will retain particles and the labeled potency will not be reduced.

ADMINISTRATION

By Syringe:

USE ASEPTIC TECHNIQUE

1. Remove cover from Profilate[®] Filter Needle package.
2. Remove protective cover from sterile disposable plastic syringe (not included).
3. Remove Profilate[®] Filter Needle aseptically from package. Insert tip of syringe into opening of Profilate[®] Filter Needle. Hold the filter as illustrated and press firmly to secure.
4. Remove cover of Profilate[®] Filter Needle by pulling cover straight off. **Do not twist or turn needle cover.**

SYRINGE — FILTER — FILTER NEEDLE — NEEDLE COVER

5. Insert Profilate[®] Filter Needle into reconstituted concentrate bottle. Inject air and aspirate the reconstituted concentrate from the bottle into the syringe.
6. Remove and discard the Profilate[®] Filter Needle from the syringe and attach syringe to a Butterfly[®] 21x¾ 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 Butterfly[®] 21x¾ 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 infusion set.
2. With bottle upright, thrust piercing pin straight through stopper center. Do not twist or angle.
3. Immediately invert bottle to automatically establish proper fluid level in drip chamber (half full).
4. Attach Butterfly[®] 21x¾ 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.

HOW SUPPLIED

Antihemophilic Factor (Human) Profilate[®] is supplied in single dose bottles, with suitable volumes of diluent. The units of AHF activity are stated on the label of each concentrate bottle.

STORAGE

Antihemophilic Factor (Human) Profilate[®] may be stored at temperatures between 2°-8°C for two years or at room temperature not exceeding 31°C for 6 months.

CAUTION: Federal (U.S.A.) law prohibits dispensing without a prescription. Single dose container for intravenous administration only.

Discard any unused contents.

Discard administration equipment after single use.

REFERENCES

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1. Wincon, E., Psychosocial aspects of hemophilia, Mt. Sinai J. Med. 44,438-455, 1977.
2. Alcdort, M., Methods of care, products available, complications of therapy, Mt. Sinai J. Med. 44:332-338, 1977.
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DATA SHEET

PROFILATE HEAT-TREATED
Wet Method

Presentation

Antihaemophilic 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 haemophilia A) or acquired Factor VIII deficiency.

Dosage and Administration

Dosage:
Antihaemophilic 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	x20x	Desired increase in Factor VIII percentage
Number of i.u. of AHF required	Body weight = in kgs	x44x	Desired increase 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 30 to 50 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, Antihaemophilic 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. Insert this exposed end of the needle through the depression in centre of the stopper in the bottle of diluent.
5. Remove plastic flip-off cap from the concentrate bottle. Tap bottle gently to dislodge concentrate from sides of bottle.
6. Swab the exposed rubber surface with alcohol. Do not leave excess cleaning agent in indentation on stopper.
7. 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.
8. 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 dissolved. 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 luer 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 Infusiuon 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, warnings, etc

Contra-Indications:
There are no known contraindications to the use of Antihaemophilic 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) by an FDA approved test. Other screening procedures are used to eliminate high risk plasma donors and a heat-treatment step in the manufacturing process is designed to reduce the risk of transmitting viral infection. However, testing methods presently available are not sensitive enough to detect all units of potentially infectious plasma and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product.

The causal factors of Acquired Immunodeficiency Syndrome (AIDS) have not been fully defined. However HTLV-III/LAV virus has been implicated as the agent of the disease. 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 may be 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 10ml/minute. More rapid administration may result in vasomotor 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 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 tendancy or hyperfibrinogenaemia. Antihaemophilic Factor (Human), Profilate, Heat-Treated does contain blood group isoagglutinins 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.

Pharmaceutical Precautions

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.

Legal Category

POM.

Package Quantities

Antihaemophilic Factor (Human), Profilate, Heat-Treated is supplied in single dose bottles with suitable volumes of diluent. The units of AHF activity expressed as International Units (i.u.), 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.

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. A newly recognised retrovirus has been implicated as a possible causative agent of AIDS. This virus has been given several names, including human T-lymphotropic virus type III (HTLV-III), Lymphadenopathy-associated virus (LAV), and AIDS – associated retrovirus (ARV) and has been commonly referred to in the literature as HTLV-III/LAV. The heat-treatment process used in the manufacture of Profilate Heat-Treated has been shown to inactivate a minimum of 3.25 logs of HTLV-III/LAV virus when the virus was intentionally added to the product. The following table shows the total number of logs of each virus inactivated.

VIRUS	LOGS INACTIVATED
HTLV-III/LAV	At least 3.25
Cytomegalovirus (CMV)	>2.0
Sindbis	4.61
Vesicular stomatitis Virus (VSV)	5.83

Chimpanzee studies demonstrate that the heat treatment step is effective in inactivating at least 500 chimpanzee infectious doses (CID) of Hepatitis B virus. Neither of two chimpanzees receiving 500 CID of Hepatitis B virus contracted Hepatitis B.

The chimpanzee study also showed that the process inactivated an undetermined quantity of at least one type of non-A, non-B hepatitis present in the Antihaemophilic Factor (Human).

Product Licence Number

P.L. 4447/0005

Address

ALPHA THERAPEUTIC UK LTD.
Unit 10, Lodge Way,
Thetford, Norfolk IP24 1HE

February 1986

2b. Examples of Warnings in Documents Provided by Baxter (Hyland/Travenol)

DATA SHEET

ANTIHAEMOPHILIC FACTOR (HUMAN) HEMOFIL METHOD FOUR

Presentation

Antihaemophilic Factor (Human), HEMOFIL Method Four is a sterile, lyophilised preparation of human antihaemophilic 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") =
$$\frac{\text{units administered}}{\text{body weight (in kg)} \times 0.4}$$

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

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 antihaemophilic 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 ground 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.

Pharmaceutical Precautions

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 haemophiliac with severe bleeding, particula , 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. 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:

Vial Size	Average Activity (I.U.)	Code Number
10 ml	250	KD-060-209
30 ml	750	KD-060-205
30 ml	1050	KD-060-207

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

hylting therapeutic products

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.[1] 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 (Hb_sAg) by counterelectrophoresis or 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 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.[2-5] 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 falling hematocrit values. The only reported case [6] showing this phenomenon is that of a young 140 pound adult surgical patient of blood group A who received 43,000 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.

Since all solutions containing fibrinogen, as does HEMOFIL® AHF Factor, tend to cause the ground 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.

Contraindications

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

The free 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 material should not be refrigerated as irreversible precipitation of active material may occur.

Storage

HEMOFIL Antihemophilic Factor (Human), Method Four, Dried, 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.

NOTE: Directions for use are provided with each product. These directions should be read and understood before testing. Particular attention should be paid to all warnings and precautions. Should you have any questions, please contact your Hyland representative.

1. Brinkhous KM, Shanbrom E, Webster WP, et al: A high potency glycine-precipitated antihemophilic factor concentrate: Use in hemophilia and hemophilia with inhibitors. JAMA 205:613, 1968
2. Dameshek W, Nober J: Transfusion reactions to a plasma constituent of whole blood. Blood 5:129, 1950
3. Mendes de Leon DE, van der Hart M: A severe plasma reaction after transfusions of blood and serum. Vox Sang 5:30, 1955
4. Hutchison JL, Freedman SO, Richards BA, et al: Plasma volume expansion and reactions after infusion of autologous and non-autologous plasma in man. J Lab Clin Med 56:734, 1960
5. Mollison PL, Blood Transfusion in Clinical Medicine, 3rd ed. Philadelphia, F. A. Davis Company, 1963, p. 541
6. Rosati LA, Barnes B, Oberman HA, et al: Hemolytic anemia due to anti-A in concentrated antihemophilic factor preparations. Transfusion 10:139, 1970

HYLAND
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THE DISCOVERY PEOPLE

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No-Charge, Direct Dial (800) 854-3235
In Alaska, California, Canada, Hawaii call (714) 540-5000

5A-100 12/75 5M

2c. Examples of Warnings in Documents

Provided by Cutter (Miles/Bayer)

Koate

Antihemophilic Factor (Human) for hemophilia A

ANTIHEMOPHILIC FACTOR (HUMAN)

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

DESCRIPTION Antihemophilic Factor (Human), Koate®, is a stable, purified, dried concentrate of human Antihemophilic Factor (Factor VIII, AHF, AHG) intended for use in therapy of classical hemophilia (hemophilia A). Koate is purified from the cold insoluble fraction of pooled fresh frozen plasma by modification and refinements of the methods first described by Hershgold, Pool and Pappenhagen.[1] Koate contains Factor VIII in concentrated and in highly purified form being some 40 to 170 times purified over whole plasma. Consequently Koate is a highly potent source of Factor VIII activity, containing approximately 25-30 times as much Factor VIII as an equal volume of fresh plasma. Relatively small volumes of Koate are needed to raise significantly the circulating level of Factor VIII activity. For example, 500 clinical units of Factor VIII (equivalent to 300 ml of fresh frozen plasma) can be administered in a volume of only 20 ml containing a total protein of about 0.5 gram. The final product when reconstituted as directed will contain 1% Dextrose (anhydrous) USP and is hypertonic.

Hemophilia A is an hereditary bleeding disease characterized by deficient activity of a specific plasma protein clotting factor, Factor VIII. The disease is sex linked being transmitted by females but occurring almost exclusively in males. In individuals so afflicted, the reduced level of Factor VIII activity may be sufficient so that hemorrhage can occur spontaneously or after only minor trauma. Surgery on such persons is not feasible without first correcting the clotting factor abnormality.

The medical management of hemophiliacs is based on replacement to the circulation of the blood clotting factor which is deficient or inactive. Prior to the availability of clotting factor concentrates, this was accomplished by transfusions of blood, fresh plasma or fresh frozen plasma. The effectiveness of these infusions is limited by the large volumes required to achieve and maintain hemostasis. The blood volume becomes expanded because of protein overload; cerebral edema, pulmonary edema, cardiac embarrassment may result.[2]

Because of these limitations, much effort has been expended by a number of investigators in separating and concentrating Factor VIII from plasma in a form suitable for substitution therapy in hemophilia A patients. A number of concentrate preparations of varying degrees of purification have evolved and have been used with clinical success. Koate is a highly purified potent concentrate which can be effectively used to increase the Factor VIII levels of patients to normal or near normal values without circulatory overload. Antihemophilic Factor (Human), Koate offers many advantages over whole blood, plasma, single unit cryoprecipitate or less potent concentrates. Among the most significant of these are: 1. Higher potency Factor VIII than cryoprecipitate or other available concentrate preparations. Therefore, adequate Factor VIII can be supplied with relatively smaller amounts of fibrinogen and other non Factor VIII proteins. This is particularly important when high circulating levels of Factor VIII must be maintained for prolonged periods, or where inhibitors must be overcome. 2. Each lot of Koate is assayed and labeled for its Factor VIII content. This permits more precise estimation of dose and prediction of effects. 3. As a lyophilized product, Factor VIII is stable in contrast to its marked decay in stored plasma. 4. Koate reconstitutes rapidly and easily and does so without excessive shaking and foam formation which can inactivate Factor VIII. 5. Being of human origin there is no danger of species antigenicity as occurs with concentrates from bovine or porcine source. 6. The high Factor VIII potency in the reconstituted product allows intravenous infusion by direct syringe injection or drip infusion without significant reactions. This permits office and home treatment. 7. Koate is free of thrombin, thromboplastin-like activity, depressor activity, and contains anti-A-anti-B blood group isoagglutinins (see discussion under Precautions). It is free of heparin and no heparin need be added before its use. THIS PRODUCT IS PREPARED FROM HUMAN VENOUS PLASMA. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN TESTED BY THE RADIOIMMUNOASSAY METHOD AND FOUND NON-REACTIVE FOR HEPATITIS B SURFACE ANTIGEN.

UNFORTUNATELY, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING.

ACTION Antihemophilic Factor (Human) is a plasma protein which corrects the coagulation defect of patients with classical hemophilia (hemophilia A). It is needed for the transformation of prothrombin to thrombin by the intrinsic pathway.

INDICATIONS Antihemophilic Factor (Human), Koate, is indicated for the treatment of classical hemophilia (hemophilia A), in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koate provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes or in order to perform emergency and elective surgery on hemophiliacs.

Antihemophilic Factor (Human) is not effective in the treatment of von Willebrand's disease.

WARNING Koate® concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products.

Kasper and Kipnis[3] have concluded that those who had little exposure to blood products had a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients.

PRECAUTIONS 1. Antihemophilic Factor (Human), Koate®, is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koate since no benefit may be expected from its use in treating other causes of hemorrhage. 2. After reconstitution, administer promptly (within 3 hours). Do not refrigerate after reconstitution. NOTE: The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koate is fully stable, without potency loss for at least 24 hours at room temperature after reconstitution. 3. Administer only by the intravenous route. 4. A filter should be used prior to administering the reconstituted Koate solution. This may be accomplished using the enclosed sterile filter needle. See Reconstitution and Administration directions. 5. Koate 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 intravascular hemolysis should be considered. 6. Administration equipment and any reconstituted Koate not used should be discarded.

ADVERSE REACTIONS No severe adverse reactions were reported during the clinical trials of Koate. One patient experienced transient chest discomfort and cough beginning 20 minutes after infusion and lasting for one hour. During subsequent infusions this patient had no further reactions. A second patient developed transient dizziness following each of eight infusions. Mild allergic reactions may result from the administration of AHF preparations.

When large or frequently repeated doses are required in patients other than those of blood type O, there is a possibility of intravascular hemolysis. Should this condition occur leading to progressive anemia, administration of serologically compatible type O packed red blood cells should be considered.[3] Also the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.[4]

DOSAGE Each bottle of Antihemophilic Factor (Human), Koate®, has the AHF activity in clinical units stated on the label of the bottle. One AHF unit is defined as the activity present in 1.0 ml of human plasma pooled from at least 10 donors and tested within three hours of collection of the first unit represented in the pool.

Dosage of Koate required for normalizing hemostasis must be individualized according to the needs of the patient. The dose is dependent upon the weight of the patient, the severity of the deficiency, the severity of hemorrhage, the presence of inhibitors, and on the Factor VIII level desired. Abildgaard *et al*[5] have reported from studies in hemophilic children a linear dose-response relation with an approximate yield of 2 percent rise in Factor VIII activity for each unit of Factor VIII per Kg of body weight transfused. Clinical experience with Koate has demonstrated an essentially identical dose response relationship.[6] The following generalized dose schedule is suggested for various clinical situations: 1. Joint hemorrhages. If aspiration is not carried out, 10 units/Kg body weight should be administered at eight to twelve hour intervals for a period of one or more days depending on severity and patient response. The latter may be measured by relief of pain, swelling and restriction of joint movement. Early joint bleeds (associated with mild pain and minimal or no swelling), if treated promptly, may respond to a single dose of 10 units/Kg.[7] If aspiration is carried out, 10 units/Kg should be administered just prior to aspiration with a similar dose given six to eight hours later and repeated as necessary. Fully developed hemarthrosis also may be treated with a single dose of 25 units/Kg aimed at achieving a Factor VIII level of 50%.[8] 2. Muscle hemorrhages. A. Minor hemorrhages in the muscles of the extremities or trunk (non-vital areas). A dose of 10 units/Kg should be administered every eight to twelve hours until pain and swelling are relieved. B. Massive hemorrhages in non-vital areas. A dose of 10 units/Kg should be infused at eight to twelve hour intervals for two days or more, depending on relief of pain, improvement in hematocrit if this has fallen, and relief of other symptoms depending on the area of hemorrhage. C. Hemorrhages near vital organs (neck, throat, subperitoneal, etc.). A 20 unit/Kg dose should be administered initially, followed by 10 units/Kg every eight hours for 48 hours. Then half the dose should be administered at those time intervals for another 48 hours or more. 3. Overt bleeding. The initial dose should be 20 units/Kg followed by 10 units/Kg every eight hours for the first 24 hours, then every twelve hours for three to four days as necessary. 4. Massive wounds. Koate® should be infused until the bleeding stops. Then a maintenance dose of 20 units/Kg should be administered every eight hours. Levels of Factor VIII should be obtained and enough Koate infused to maintain a minimum Factor VIII level of 40% in the patient. 5. Surgery.[9,10,11] Factor VIII levels of at least 40% are required for surgery. For surgery in the central nervous system even higher levels are recommended. Thirty to forty units/Kg body weight should be administered prior to surgery followed by 20 units/Kg every eight hours after surgery. This should be done with laboratory control, and the dosage should be increased if the Factor VIII level falls below 30% just prior to the next infusion. The postinfusion level should be approximately 60%, and it has been suggested that the Factor VIII level be raised to 30 to 40% of normal for at least ten days postoperatively.[12] For each unit of anti-hemophilic factor administered per Kg of body weight, a 2% rise in Factor VIII activity has been observed.[7] The following formulae can therefore be used to calculate approximately the expected response from a given dose or the dose required for a given effect:

Expected Factor VIII increase (in % of normal) =

$$\frac{2.0 \times \text{units administered}}{\text{body weight (in Kg)}}$$

Units required = body weigh (Kg) X desired Factor VIII increase (% normal) X 0.5

It should be emphasized however, that all efforts should be made to follow the course of therapy with Factor VIII level assays. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained. 6. Prophylaxis. Experience with Factor VIII in the prophylactic management of severe hemophilia A has been published.[13,14,15] Kasper *et al*[14] have recommended a dosage of 250 units of Factor VIII per day in the morning for patients weighing less than 50 Kg, and 500 units of Factor VIII for heavier patients. If bleeding episodes still occur too frequently, the daily dose is progressively increased until a satisfactory degree of protection is obtained.

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® 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 F tor VIII inhibitor should be suspected. By appropriate labc tory procedures the presence of an inhibitor can be substa ated and quantified thus allowing calculation of the amount Factor VIII needed for its neutralization. When inhibitor is p ent, the dosage requirements for Factor VIII are extremely v able, and the dosage can be determined only by the clini response.

RECONSTITUTION AND ADMINISTRATION 1. Warm opened diluent (Sterile Water for Injection, USP) and tihemophilic Factor (Human), Koate, to room temperature, not higher than 37°C (99°F). 2. Remove the plastic flip-top c from both bottles to expose the central portions of the rubl stoppers and cleanse each stopper with a suitable antisep immediately before each piercing. We recommend the follow procedure: First swab the stopper with Iodine Tincture, USP lowed by a sterile antiseptic swab. 3. With a sterile needle syringe withdraw the appropriate volume of diluent and trans to the bottle of lyophilized Koate®. The Koate bottle is not sea under vacuum. Add the Sterile Water for Injection, USP dilu gently so as to avoid excessive foaming. Do not bleed out either before or after reconstitution. 4. Withdraw needle fr the concentrate bottle stopper and gently agitate the bottle fr time to time until the Koate powder is completely dissolved. constitution usually requires less than 5 minutes. 5. After concentrate powder is completely dissolved withdraw the Ko solution into the syringe *through the filter needle* which supplied in the package. Replace the filter needle with an app priate sterile injection needle, e.g., 21 gauge X 1 inch, and inj intravenously. 6. If the same patient is to receive more than bottle of Koate the contents of two bottles may be drawn into same syringe through filter needles before attaching the needle. Additional bottles may be drawn into the same syri through filter needles supplied.

STORAGE Antihemophilic Factor (Human), Koate, should stored under refrigeration (2° to 8°C; 35° to 46°F). Storage lyophilized powder at room temperature (up to 25°C or 77°F) six months, such as in home treatment situations, may be de without loss of Factor VIII activity. Freezing should be avoided breakage of the diluent bottle might occur. Reconstituted Ko should not be refrigerated and should be used within three ho of reconstitution.

HOW SUPPLIED Antihemophilic Factor (Human), Koate, supplied in single dose bottles with the total units of Factor V activity and total grams of protein stated on the label of e bottle. A suitable volume of Sterile Water for Injection, USP, a sterile filter needle is provided.

LIMITED WARRANTY A number of factors beyond our cont could reduce the efficacy of this product or even result in an effect following its use. These include storage and handling the product after it leaves our hands, diagnosis, dosage, met of administration, and biological differences in individual tients. Because of these factors, *it is important that this prod be stored properly and that the directions be followed caref during use, and that the risk of transmitting hepatitis be caref weighed before the product is prescribed.*

No warranty express or implied, including any warranty merchantability or fitness is made. Representatives of the C pany are not authorized to vary the terms or the contents of printed labeling including the package insert, for this pred except by printed notice from the Company's Berkeley, Cali nia office. Prescriber and user of this product must accept terms hereof.

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Cutter Biological

Cutter Laboratories, Inc., Berkeley, Calif. 94710, U.S.
Printed in U.S.A.

DATA SHEET

NAME OF PRODUCT

KOATE*–HT
Dried Factor VIII Fraction Heat-treated

PRESENTATION

Koate–HT is a stable purified dried concentrate of human Factor VIII (Antihaemophilic 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 the 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. Insert exposed needle into stopper of diluent bottle.
4. Remove the protective plastic from the other end of the needle. Invert the diluent bottle and insert exposed needle into stopper of the concentrate bottle.
5. The vacuum will transfer the diluent into the concentrate bottle. Hold the concentrate bottle at an angle to the diluent bottle in order to direct the jet of diluent against the wall of 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.

CONTRA INDICATIONS, WARNINGS, ETC.

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 hyperfibrogenaemia.
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.

PHARMACEUTICAL PRECAUTIONS

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

P.O.M.

PACKAGE QUANTITIES

Each pack contains:–

One single-dose vial of Factor VIII Fraction containing approximately 250, 500, 1,000 or 1,500 IU's, one vial of the appropriate quantity of Water for Injection, a sterile filter needle and a sterile double-ended transfer needle.

FURTHER INFORMATION

After infusion of Factor VIII, there is an instantaneous rise in the coagulant level, followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity. The early rapid phase may represent the time of equilibrium with the extravascular compartment, and the second or slow phase of the survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused Factor VIII. Studies with Koate–HT in haemophiliacs have demonstrated an initial 50% disappearance time of five hours, and a biologic half-life of approximately 13 hours. There were not significant differences between bleeding and non-bleeding patients.

Koate–HT has been heated at 68°C for 72-77 hours and there is no evidence of any adverse effect upon the properties of the product. The heat treatment step has been introduced to reduce the risk of transmission of infectious agents.

Studies have demonstrated that the heat-treatment process used in the production of Koate–HT inactivates potential infectious viruses, including a retrovirus, but it has not yet been established that agents of any major transmittable disease would be inactivated.

PRODUCE LICENCE No.

PL 0055/0107

NAME AND ADDRESS OF LICENCEE

Cutter Division,
Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
Berkshire,
SL2 4LY

Cutter

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

February 1985

Konyne®

Factor IX Complex (Human) (Factors II, VII, IX, and X) for hemophilia B

FACTOR IX COMPLEX (HUMAN) (FACTORS II, VII, IX AND X)
Konyne®

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

DESCRIPTION FACTOR IX COMPLEX (HUMAN) (FACTORS II, VII, IX and X) Konyne® is a stable dried purified plasma fraction comprising coagulation factors II, VII, IX and X with a minimal amount of total protein. It is intended for use in the treatment of congenital factor IX deficiency (hemophilia B), congenital factor VII deficiency, congenital factor X deficiency, and in other bleeding disorders resulting from an acquired deficiency of factors II, VII, IX, and X.

Factor	*Common Synonyms*
II	Prothrombin
VII	Proconvertin
IX	Plasma Thromboplastin Component PTC Christmas Factor
X	Stuart Factor

Each bottle of Konyne® concentrate contains approximately 500 units of factor IX, as well as amounts of factors II, VII, and X, roughly proportionate to their respective levels in average fresh plasma. One unit of factor IX (or II, VII or X) is equivalent to the activity found in one ml of fresh normal plasma. Therefore, a 500 unit bottle of Konyne® concentrate is equivalent to at least two packages of fresh frozen plasma (FFP). The product is standardized in terms of factor IX.

The specific activity is never less than 0.7 unit per mg protein and is generally about 1.0 unit per mg protein, which represents a 60-fold concentration in terms of plasma protein. Thus 1000 units (equivalent to one liter of FFP) can be administered in a volume of only 40 ml containing only one gram of protein.

Konyne® concentrate is free of thrombin, thromboplastin-like activity, anti-complement activity, and depressor activity. It is free of heparin. Anti-A and anti-B agglutinins are in the range of 1:32 or below; this is considered a clinically insignificant level and the product may be safely used without typing or crossmatching.

THIS PRODUCT IS PREPARED FROM HUMAN VENOUS PLASMA. EACH INDIVIDUAL UNIT OF PLASMA HAS BEEN FOUND NON-REACTIVE FOR HEPATITIS B SURFACE ANTIGEN USING THE RADIOIMMUNOASSAY METHOD.

UNFORTUNATELY, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING.

ACTIONS (Role of Factors II, VII, IX and X) All four factors are synthesized in the liver and are vitamin K dependent. (Factor V is also produced in the liver, but is not vitamin K dependent.) Congenital deficiencies of each of the four factors do occur in the absence of liver disease, and each results in a hemorrhagic condition. Hereditary deficiency of factor II (prothrombin) is extremely rare. Acquired deficiencies of II on the other hand are common and are almost always associated with deficiencies of VII, IX, and X as well.

Severe congenital deficiency of factor VII is also rare, about 1 in 400,000, but partial deficiency is more common. A severe deficiency of VII causes a prolonged one-stage prothrombin time, but the patient exhibits a normal clotting time and normal PTT and TGT.

Factor X resembles factor VII in many respects. Both show a similar incidence of congenital deficiency, both are essential to a normal one-stage prothrombin time, and both are low in liver disease and in vitamin K deficient states. However, the clotting time of blood deficient in factor X is very prolonged, in contrast to the clotting time of blood deficient in VII. As many people as 1 in 500 may be heterozygous for the defective genes associated with VII or X deficiency and thereby be mildly affected. Heterozygotes, especially females, may bleed excessively in times of stress. It is important to remember that most of the information on published prior to 1956 relates not to VII as such, but to the properties of VII plus X.

The recognition and characterization of factor IX in 1952 allowed the discrimination between hemophilia A and hemophilia B.[1,2,3] For the classic modern treatise on the hemophilias, the reader is referred to Biggs and Macfarlane.[4]

The incidence of severe congenital deficiency of factor IX (hemophilia B) is in excess of 1 in 100,000, and the incidence of a partial deficiency with bleeding tendencies is much higher. It is impossible to differentiate between hemophilia A and hemophilia B on clinical grounds alone, and there is a large proportion of mild cases of hemophilia B which easily escape recognition.

When the four factors are considered together, factor X plays the key role in the clotting mechanism. In the intrinsic clotting system, factor IX is essential for activating factor VIII which, in turn, activates factor X. In the extrinsic clotting system, factor X is activated directly by factor VII and tissue thromboplastin. Activated factor X causes the explosive conversion of factor II (prothrombin) to its activated form (thrombin).

INDICATIONS In general, the administration of FACTOR IX COMPLEX (HUMAN) (FACTORS II, VII, IX and X)-Konyne® is indicated whenever one or more of the specific coagulation factors II, VII, IX, X must be elevated in order to correct or prevent a dangerous bleeding episode or in order to perform surgery. 1. Demonstrated factor IX deficiency in children or adults (hemophilia B; Christmas Disease) with real or impending bleeding episodes. Spontaneous bleeding may be into joints, or soft tissues. The bleeding may also be due to trauma. 2. Demonstrated factor II, VII or X deficiency, in the same situations as above. 3. Only under life threatening circumstances, Konyne® concentrate is indicated in the treatment of infants with significant hemorrhage due to Hemorrhagic Disease of the Newborn with proven deficiency of factors II, VII, IX and X. 4. Also, only under life threatening circumstances, Konyne® concentrate is indicated in the treatment of children or adults with acquired hepatic insufficiency with proven deficiency of factors II, VII, IX, X, who are either bleeding or are being considered for surgical intervention. (See Precautions.)

CAUTION: BECAUSE OF THE HEPATITIS RISK, THE USE OF KONYNE® CONCENTRATE IN LIVER DISEASE MUST BE CONSIDERED ONLY IN CASES WHERE THE EXPECTED BENEFICIAL EFFECTS FAR OUTWEIGH THE POTENTIAL HAZARD OF SUPERIMPOSING A VIRAL HEPATITIS ON AN ALREADY DAMAGED LIVER. FURTHERMORE, DUE TO THE HEPATITIS RISK, THE INDISCRIMINATE USE OF KONYNE® AS A PRECAUTIONARY THERAPEUTIC PROCEDURE IN PATIENTS NOT HAVING THE PREVIOUSLY DISCUSSED SPECIFIC INDICATIONS IS NOT RECOMMENDED.

Kasper and Kipnis[5] have concluded that those who had little exposure to blood products had a high risk of developing hepatitis after introduction of clotting factor concentrates. They recommend for those patients, especially those with mild hemophilia, single donor products. However, for patients with severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients.

Note: For publications on the clinical use of Konyne® concentrate, the reader is referred to references[6-16]

CONTRAINDICATIONS Do not use in cases of known liver disease where there is any suspicion of intravascular coagulation or fibrinolysis.

WARNING Hepatitis Konyne® concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. **The presence of hepatitis virus should be assumed and the hazard of administering Konyne® concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products.**

Thrombosis Cases of patients developing postoperative thrombosis after treatment with Factor IX complex concentrates have been described. Although thrombosis is a well-known risk of postoperative period, it was found to be higher in these patients.[2] No other data is presently available. Until further surveys and more conclusive studies are available, Konyne® concentrate is not advised for patients undergoing elective surgery, unless the expected beneficial effects of its use outweigh the increased risk of the possibility of thrombosis. This especially applies to those who may be predisposed to thrombosis. In emergency cases and where large quantities of Konyne® concentrate are needed, however, use of one of the established prophylactic anticoagulant regimens may be considered.

Since there is this definite risk of hepatitis, we suggest that the physician give consideration to explaining to the patient (or the patient's family) the relative risks of giving or withholding this product. Then, should the patient develop hepatitis as a result of the injection, it will not come as a surprise, and there is not nearly the likelihood of resentment, which will almost surely follow an unexplained and unexpected infection.

PRECAUTIONS 1. Patients who receive Konyne® concentrate post-operatively or with known liver disease should be kept under close observation for signs and symptoms of intravascular coagulation. Any suspicious findings of this nature should indicate prompt discontinuation of therapy. 2. After reconstitution, administer promptly. 3. Reconstitute only with Sterile Water for Injection, USP. 4. Administer only by the intravenous route. 5. Do not reconstitute and administer in a concentration greater than 50 units per ml. 6. The syringe or administration set, and any reconstituted Konyne® concentrate not immediately used, should be discarded.

Note: The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any bacterial contamination occurring during reconstitution. FACTOR IX COMPLEX (HUMAN) (FACTORS II, VII, IX and X)—Konyne® is stable for at least 12 hours at room temperature after reconstitution.

ADVERSE REACTIONS In some patients, the rapid administration of Konyne® concentrate can cause, on rare occasions, transient fever, chills, headache, flushing, or tingling.

DOSAGE Each bottle of Konyne® concentrate has the Factor IX activity in clinical units stated on the bottle label. One unit is being defined as the activity present in 1 ml of average normal fresh plasma. The potency is adjusted in terms of factor IX since it has been demonstrated that the other factors (II, VII, X) are present in approximately the same amount.

The amount of Konyne® concentrate required for normalizing hemostasis will depend on the patient and on the circumstances, and it is preferable by far to have the appropriate coagulation assays performed prior to treatment and at suitable intervals during treatment.

Some guidelines can be suggested as the result of clinical experience to date with Konyne® concentrate.

1. In factor IX deficient patients, whether bleeding or non-bleeding, administration of 2 units per Kg of body weight will cause an average in-vivo increase of 35% (range = 1.7%-5.0%) when measured 15 minutes after administration. 2. In factor VII deficient patients, whether bleeding or non-bleeding, administration of 2 units per Kg of body weight will cause an average in-vivo increase of 4% (range = 2.5%-5.4%) when measured 15 minutes after administration. 3. In factor VII and factor IX deficient patients undergoing extensive surgical or dental procedures, the levels of factor VII or factor IX should be maintained above 20% of normal. An initial large dose, resulting in a level of approximately 60%, makes it easier to maintain hemostatic levels later using smaller and fewer doses. A critical period is about 5 days post surgery, and full protection should be provided for about 8 days. Each patient presents a special problem, and no specific directions can be given.

PROPHYLAXIS The ideal treatment for proven congenital deficiency of the procoagulants would be prophylactic administration. In a study of three adults with clinically severe factor IX deficiency, a prophylactic schedule of 500 units I.V. every week has been effective in preventing spontaneous bleeding episodes. A prophylactic schedule of 500-1,000 units every two weeks was insufficient to prevent all spontaneous bleeding episodes but did greatly lessen their severity and kept the patients free of hospitalization. Additional Konyne® concentrate should be given when a patient on prophylaxis is exposed to trauma. One must assume that each patient should be adjusted to his proper prophylactic dose.

Attempts at prophylactic maintenance of two adults with severe factor VII deficiency were not so successful. A schedule of 1,500 units I.V. every week was insufficient to prevent all spontaneous bleeding episodes although the patients were free of hospitalization during the 8-month study period. However, Marder and Shulman[9] achieved successful prophylactic maintenance of one patient, using a different Factor VII concentrate[11] administered in a smaller dose but given twice a week.

Prophylactic maintenance of patients with severe factor II or factor X deficiency would appear ideal because of the long post-infusion half-life of factors II and X. However, the incidence is so uncommon that studies of prophylaxis have not been made.

OVERDOSAGE CAUTION: Do not overdose. Factor X has a long post-infusion half-life. Repeated administrations generally result in successively larger increases in blood levels, particularly of factors IX and X. Without careful monitoring of the patient's levels of II, IX, and X, unnecessarily high levels can occur, the result of which may increase the risk of intravascular coagulation.

RECONSTITUTION AND ADMINISTRATION 1. Reconstitution will be more rapid if the diluent bottle is warmed to room temperature. Do not warm above 40° C. (104° F). 2. Remove the plastic flip-top caps from the concentrate and the diluent bottles to expose the central portions of the rubber stoppers. 3. Cleanse stoppers with germicidal solution. The Konyne® concentrate bottle is not sealed under vacuum. Reconstitution with 20 ml of the accompanying diluent is recommended, although reconstitution with no less than 10 ml can be effected if desired. 4. With a sterile needle and syringe, withdraw 20 ml of diluent and transfer to the bottle of lyophilized Konyne® concentrate. Add the water gently so as to avoid excessive foaming. Do not bleed out air either before or after reconstitution. 5. Gently agitate the bottle from time to time until the powder is dissolved. Reconstitution usually requires two minutes or less. 6. After the concentrate powder is completely dissolved withdraw the Konyne solution into the syringe *through the filter needle* which is supplied in the package.

STORAGE FACTOR IX COMPLEX (HUMAN) (FACTORS II, VII IX and X)—Konyne® should be stored under refrigeration (2° to 8° C.; 35° to 46° F). Freezing should be avoided as breakage of the diluent bottle might occur.

Konyne® concentrate may be stored for a period of up to one month at temperatures not to exceed 37° C (99° F) during travel.

HOW SUPPLIED Konyne® concentrate is supplied in single dose bottles with the total units of factor IX activity stated on the label of each bottle. A suitable volume of Sterile Water for Injection, USP, and a sterile filter needle are provided.

LIMITED WARRANTY A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use, and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed.

No warranty express or implied, including any warranty of merchantability or fitness is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labeling, including the package insert, for this product except by printed notice from the Company's Berkeley, California Office. Prescriber and user of this product must accept the terms hereof.

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Cutter Laboratories, Inc., Berkeley, Calif. 94710. U.S.A.
Printed in U.S.A.

2d. Examples of Warnings in Documents

Provided by Immuno Ltd.

KRYOBULIN™ IMMUNO LIMITED

Dried Human Antihaemophilic Fraction B.P.

DATA SHEET

name of product: KRYOBULIN™
Dried Human Antihaemophilic Fraction B.P.

presentation: Dried Human Antihaemophilic Fraction is a white to yellowish amorphous powder or friable solid without any characteristic odour.

It is prepared from the plasma of donors whose transaminase levels are constantly checked and whose donations are shown by R.I.A. to be free from HB_sAg. Pooled plasma and the final product are also tested for freedom from HB_sAg.

It is packed in vials each containing approximately 250,500 or 1000 International Units of Factor VIII. Separate vials of solvent are also provided, these being Water for Injections B.P.

1 International Unit is the amount of Factor VIII activity contained in 12.745 mg of the 2nd International Standard for Blood Coagulation Factor VIII Human. It is approximately equivalent to the Factor VIII activity in 1 ml. of average normal plasma.

uses: Kryobulin corrects Factor VIII deficiency, and is used in the treatment of bleeding due to such deficiency in:

- Haemophilia A
- von Willebrand's disease
- Haemophilia complicated by Factor VIII inhibitors

dosage and administration: Frequent tests of the patient's plasma level of Factor VIII must be made to allow correction of the deficiency by Kryobulin administration, but for guidance an estimation of the required dosage can be made by the following calculation:

To achieve an increase of Factor VIII concentration of 1% it is necessary to administer 1 i.u. of Kryobulin per kg. bodyweight, both for adults and children.

Initial treatment requires doses to be given at shorter intervals than in maintenance therapy, to provide an initial high level of activity and to replenish the extravascular compartment.

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 eight 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 till 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.

contra indications warnings, etc.:

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.

pharmaceutical precautions:

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 I/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, name and address:

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.

PROTHROMPLEX™
Partial Prothrombin Complex (Human)

IMMUNO LIMITED

DATA SHEET

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 HB_sAg. Pooled plasma and the final product are also tested by RIA for freedom from HB_sAg. 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.

dosage and administration : 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 Antihaemophilic 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.

CLINICAL Manifestation	Therapeutically wanted minimum Factor IX level	Initial dose in units Factor IX per kg bodyweight	Maintenance dose at intervals of 6 to 12 (24) hours in units Factor IX per kg bodyweight
surface bleedings of the skin and mucosae			
superficial or deep haematoma			
haemarthoses	5 - 10%	15 U	7 - 15 U
slight bleedings following injuries			
uncomplicated dental extractions			
severe muscle haematoma			
moderate bleedings following injuries			
gastric and intestinal haemorrhages			
bone fractures	15 - 30%	20 - 30 U	15 - 30 U
cerebral bleedings			
haematuria			
complicated dental extractions			
minor surgery			
major surgery	more than 50%	75 U	50 - 75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy the 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 rashes to severe anaphylactic shock are possible when human plasma derivatives are adminstered. 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 $+2^{0}$ C and $+6^{0}$ 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 :

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0215/006
007

Product Licence Holder:
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Tel. No: Sevenoaks (0732) 58101 & 50342
Telex No. 95413

date of preparation : May 1979

Prothromplex is a trade mark