PF

Armour Pharmaceutical Company Limited

St. Leonards House, St. Leonards Road, Eastbourne, Sussex BN21 3YG
Telephone: Eastbourne (0323) 21422 Telex: 87141

AI000093

ASC/tb/1161/86

9 January 1986

Department of Health and Social Security
Market Towers
1 Nine Elms Lane
Vauxhall
LONDON
SW8 5NQ

Dear Sirs

FACTORATE HEAT TREATED - PL 0231/0038
HIGH POTENCY FACTORATE HEAT TREATED - PL 0231/0044

Please find enclosed applications to vary the above Product Licences.

Thank you for your attention to this matter.

Yours faithfully
ARMOUR PHARMACEUTICAL COMPANY LIMITED

GRO-C

A S Clark (Miss)
Registration Officer

Encs

MEDICINES ACTS 1968 AND 1971

FORM MLA 221
(Revised 1984)

APPLICATION TO CHANGE TO PRODUCT LICENCE

Licence Number: 0231/0038

Product Name: FACTORATE HEAT TREATED

Name and Address of Licence Holder:
Armour Pharmaceutical Company Limited
St Leonards House
St Leonards Road
EASTBOURNE
East Sussex
BN21 3YG

AI000094/1

Telephone Number: (0323) 21422, Ext GRO-C
Your reference: R86/4

3. Please indicate if you have changed or propose to change any of the following:

- ☐ Name of Product
- ☐ Pharmaceutical Form
- ☐ Manufacturer
- ☐ Date of Expiry of Licence
- ☐ Active Ingredients
- ☐ Indications
- ☐ Dosage
- ☐ Contraindications and warnings
- ☐ Method of Retail Sale and Supply
- ☐ Activities covered by Licence
- ☐ Assembler
- ☐ Arrangements for Storage
- ☐ Container
- ☐ Shelf Life or Storage Precautions
- ☐ Method of manufacture
- ☐ Quality Control Procedures
- ☐ Finished Product Specification
- ☐ Constituent Specification
- ☐ Excipients
- ☐ Supplier of Active Ingredients
- ☒ Other (Specify)
  Additional information on data sheet.

4. On the attached sheet, give the present particulars, the change or proposed change and the reason. Any supporting evidence should be attached to the application. Please indicate the number of volumes and number of copies sent. Where the licensee has already completed MLA 201R or the latest versions of MLA 201 or MLA 231 (ie Revised 1984) it would be helpful if 3 corrected copies of the appropriate page could also be attached.

5. For Licensing Authority Only:

Application dated.....
Received.....
Acknowledged.....
Stats ref.....
Code.....

Route:

Pharm:

Med:

Application Approved

Pharmacist:
Date:
Doctor:

Name of Product: FACTORATE HEAT TREATED Licence Number: 0231/0038

Address for reply:

AI000094/2

Miss A S Clark
Registration Officer
Armour Pharmaceutical Company Limited
St Leonards House St Leonards Road
EASTBOURNE East Sussex BN21 3YG

Give the present product particulars and proposed change. If the change refers to particulars on the Schedule of the product licence you should give them exactly as they currently appear on the licence and how you propose they should be stated (continue on a separate sheet if necessary). Please attach supporting evidence to the application and indicate the number of volumes and copies.

Present	Proposed
Presentation Dried Human Antihaemophilic Fraction Factorate Heat Treated is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma. Each vial contains the labelled amount of antihaemophilic activity in International Units (one International Unit is the activity equivalent to the average Factor VIII content of 1ml aliquots of 167 samples of fresh normal plasma, as determined in an international /cont	Presentation As at present but additionally the following information to be included: "All units of source plasma are tested for antibodies to human T cell lymphotropic virus type III (HTLV III) and found to be negative." Proposed data sheet text attached. Reason This test is now being carried out routinely on all plasma collected.

I hereby make application for the above licence to be changed in accordance with the proposals given above and certify that the changes will not adversely affect the quality of the product.

Signed GRO-C Date 9 January 1986

Status Registration Officer

The licensing authority *consents to/acknowledges your request to change the product licence as outlined at 8 above.

Please retain this form with the formal documents relating to the product licence as evidence of *approval/notification of the change.

Signed: Date:

A person authorised to sign
on behalf of the Secretary of
State for Social Services

*Delete as appropriate

Present

Presentation (continued)

collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when Water for Injections BP is added as directed.

This product has been heated at 60°C for 30 hours. This step has been introduced in order to reduce the risk of transmission of infectious agents.

PRESENTATION

Dried Human Antihaemophilic Fraction Factorate Heat Treated is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma.

Each vial contains the labelled amount of antihaemophilic activity in International Units (one International Unit is the activity equivalent to the average Factor VIII content of 1 ml aliquots of 167 samples of fresh normal plasma, as determined in an international collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when Water for Injections BP is added as directed.

This product has been heated at 60°C for 30 hours. This step has been introduced in order to reduce the risk of transmission of infectious agents.

All units of source plasma are tested for antibodies to human T cell lymphotropic virus type III (HTLV III) and found to be negative.

USES

For use in therapy of classic haemophilia (Haemophilia A).

DOSAGE AND ADMINISTRATION

Factorate Heat Treated is for intravenous administration only. As a general rule one unit of Factor VIII activity per kg will increase by 2% the circulating Factor VIII level, and although dosage must be adjusted according to the needs of the patient (weight and severity of haemorrhage, presence of inhibitors) the following general dosages are suggested.

1. **Overt bleeding:** Initially 20 units per kg of body weight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for the next 3 or 4 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.

2. **Muscle haemorrhages:**

   (a) Minor haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.

   (b) Massive haemorrhages in non-vital areas: 10 units per kg by infusion at 12 hour intervals for 2 days and then once a day for 2 more days.

   (c) Haemorrhages near vital organs (neck, throat, subperitoneal): 20 units per kg, initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one half.

3. **Joint haemorrhages:** 10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

4. **Surgery:** Dosages of 30 to 40 units per kg body weight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post-operatively is suggested.

5. **Dental extractions:** For simple extractions a pre-operative dose of 20-25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation.

Recommended reconstitution:

Reconstitute Factorate Heat Treated using the appropriate quantity of Water for Injections BP as shown below using standard aseptic precautions.

Nominal amount of antihaemophilic activity (International Units)	**Quantity of Water for Injections BP**
	(ml)
250	20 (10*)
500	40 (20*)
1000	60 (30*)

*In some circumstances, where a small volume is required, it may be preferable to reconstitute Factorate Heat Treated with a lower volume of Water for Injections BP, however the content of sodium and citrate ions will not comply with the BP. These volumes are given in brackets in the table above.

Warm both diluent and Factorate Heat Treated vials to between 20°C and 25°C. Direct diluent down the side of the vial and gently rotate the vial until contents are dissolved. DO NOT SHAKE VIAL. Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes less than 5 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used.

Administration: Standard aseptic techniques should be used at all times.

Intravenous injections: Plastic disposable syringes are recommended with Factor VIII solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of Factor VIII vial; inject air and withdraw the reconstituted solution from the vial.

2. Discard the filter needle and attach a suitable intravenous needle.

3. Administer solution by slow intravenous injection (20 ml in about five minutes).

Intravenous infusion: The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2463: 1962, Transfusion Equipment for Medical Use.

1. Prepare solution of Factorate Heat Treated as recommended under 'Reconstitution'.

2. Attach suitable infusion set.

3. If more than one vial is to be administered to the same patient the infusion set may be transferred to a second vial.

4. When infusion of Factorate Heat Treated is complete, the infusion set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.

5. After use, discard infusion set, needles and vials together with any unused solution.

CONTRA-INDICATIONS, WARNINGS, ETC.

Warning: Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

Side-effects: Products of this type are known to cause mild chills, nausea or stinging at the infusion site.

Contra-indications: There are no known contra-indications to antihaemophilic fraction.

Precautions: Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of a haematocrit and direct Coombs test for signs of progressive anaemia.

PHARMACEUTICAL PRECAUTIONS

Factorate Heat Treated is to be stored at refrigerator temperature (2°C - 6°C). When stored as directed, it will maintain its labelled potency for the dating period indicated on the label but within this period may be stored at room temperature (not exceeding 30°C or 86°F) for up to six months.

LEGAL CATEGORY

POM

PACKAGE QUANTITIES

Factorate Heat Treated is supplied in single dose vials (potency is stated on each vial label).

FURTHER INFORMATION

Haemophilia A, a hereditary disorder of blood coagulation occurring almost exclusively in males results in profuse bleeding in joints, muscles or internal organs as a result of minor trauma. The disease appears to be due to a deficiency of a specific plasma protein, antihaemophilic factor, Factor VIII: Factorate Heat Treated provides temporary replacement of the missing clotting factor.

Affected individuals frequently require therapy following minor trauma. Surgery, when required in such individuals must be preceded by temporary correction of the clotting abnormality with fresh plasma transfusion, cryoprecipitate or by injections of Factor VIII concentrates. Obvious advantages of the use of concentrates of Factor VIII are the avoidance of hyper-proteinaemia, overloading the circulatory system and possible kidney dysfunction resulting from large volume transfusions.

Several different concentrations of Factor VIII have been used successfully. These range from Fraction 1 of Cohn to highly purified potent preparations. Dried Human Antihaemophilic Fraction - Factorate Heat Treated is an intermediate category, being purified cryoglobulin complying with the standards of the BP.

PRODUCT LICENCE NUMBER 0231/0038

MEDICINES ACTS 1968 AND 1971

FORM MLA 221
(Revised 1984)

APPLICATION TO CHANGE TO PRODUCT LICENCE

. Licence Number: 0231/0044 Product Name: HIGH POTENCY FACTORATE HEAT TREATED

. Name and Address of Licence Holder: Armour Pharmaceutical Company Limited
St Leonards House
St Leonards Road
EASTBOURNE
East Sussex
BN21 3YG

AI000095/1

Telephone Number: (0323) 21422, Ext GRO-C
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Application Approved

Pharmacist:
Date:

ARMOUR001616

ARMO0000181_0009

Name of Product: HIGH POTENCY FACTORATE HEAT TREATED Licence Number: 0231/0044

Address for reply:

Miss A S Clark
Registration Officer
Armour Pharmaceutical Company Limited
St Leonards House St Leonards Road
EASTBOURNE East Sussex BN21 3YG

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A person authorised to sign
on behalf of the Secretary of
State for Social Services

*Delete as appropriate

Presentation (continued)

aliquots of 167 samples of fresh normal plasma, as determined in an international collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when Water for Injections BP is added as directed.

This product has been heated at 60°C for 30 hours. This step has been introduced in order to reduce the risk of transmission of infectious agents.

HIGH POTENCY FACTORATE HEAT TREATED

PRESENTATION

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1. **Overt bleeding:** Initially 20 units per kg of body weight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for the next 3 or 4 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.

2. **Muscle haemorrhages:**

   (a) Minor haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.

   (b) Massive haemorrhages in non-vital areas: 10 units per kg by infusion at 12 hour intervals for 2 days and then once a day for 2 more days.

   (c) Haemorrhages near vital organs (neck, throat, subperitoneal): 20 units per kg, initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one half.

3. **Joint haemorrhages:** 10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

4. **Surgery:** Dosages of 30 to 40 units per kg body weight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post-operatively is suggested.

5. **Dental extractions:** For simple extractions a pre-operative dose of 20-25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation.

Recommended reconstitution:

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Nominal amount of antihaemophilic activity (International Units)	**Quantity of Water for Injections BP**
	(ml)
250	10
500	20
1000	30
2000	60

Warm both diluent and High Potency Factorate Heat Treated vials to between 20°C and 25°C. Direct diluent down the side of the vial and gently rotate the vial until contents are dissolved. DO NOT SHAKE VIAL. Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes approximately 10 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used. The solution should be used within 3 hours of reconstitution.

Administration: Standard aseptic techniques should be used at all times.

Intravenous injections: Plastic disposable syringes are recommended with Factor VIII solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of Factor VIII vial; inject air and withdraw the reconstituted solution from the vial.

2. Discard the filter needle and attach a suitable intravenous needle.

3. Administer solution by slow intravenous injection, at a rate comfortable to the patient and not exceeding 2 ml per minute.

Intravenous infusion: The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2463: 1962, Transfusion Equipment for Medical Use.

1. Prepare solution of High Potency Factorate Heat Treated as recommended under 'Reconstitution'.

2. Attach suitable infusion set.

3. If more than one vial is to be administered to the same patient the infusion set may be transferred to a second vial.

4. When infusion of High Potency Factorate Heat Treated is complete, the infusion set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.

5. After use, discard infusion set, needles and vials together with any unused solution.

CONTRA-INDICATIONS, WARNINGS, ETC.

Warning: Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

Side-effects: Products of this type are known to cause mild chills, nausea or stinging at the infusion site.

Contra-indications: There are no known contra-indications to antihaemophilic fraction.

Precautions: Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of a haematocrit and direct Coombs test for signs of progressive anaemia.

PHARMACEUTICAL PRECAUTIONS

High Potency Factorate Heat Treated is to be stored at refrigerator temperature (2°C - 6°C). When stored as directed, it will maintain its labelled potency for the dating period indicated on the label but within this period it may be stored at room temperature (not exceeding 30°C or 86°F) for up to six months.

LEGAL CATEGORY

POM

PACKAGE QUANTITIES

High Potency Factorate Heat Treated is supplied in single dose vials (potency is stated on each vial label).

FURTHER INFORMATION

Haemophilia A, a hereditary disorder of blood coagulation occurring almost exclusively in males results in profuse bleeding in joints, muscles or internal organs as a result of minor trauma. The disease appears to be due to a deficiency of a specific plasma protein, antihaemophilic factor, Factor VIII: High Potency Factorate Heat Treated provides temporary replacement of the missing clotting factor.

Affected individuals frequently require therapy following minor trauma. Surgery, when required in such individuals must be preceded by temporary correction of the clotting abnormality with fresh plasma transfusion, cryoprecipitate or by injections of Factor VIII concentrates. Advantages of the use of concentrates of Factor VIII are the avoidance of hyper-proteinaemia, overloading the circulatory system and possible kidney dysfunction resulting from large volume transfusions.

Several different concentrations of Factor VIII have been used successfully. These range from Fraction 1 of Cohn to highly purified potent preparations. Dried Human Antihaemophilic Fraction - High Potency Factorate Heat Treated is a purified preparation with lower levels of fibrinogen and other non-AHF protein per international unit than 'Intermediate Purity' AHF preparations.

PRODUCT LICENCE NUMBER 0231/0044