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APPLICATION FOR A PRODUCT AUTHORISATION

FOR

F A C T O R A T E

(DOUBLE FILL PRESENTATION) **AP000074**

PART I - SUMMARY

Armour Pharmaceutical Company Limited, Eastbourne, Sussex

ARMOUR000778

ARMO0000091_0001

APPLICATION FOR A PRODUCT AUTHORISATION

FOR

F A C T O R A T E

(DOUBLE FILL PRESENTATION)

PART I SUMMARY

WJT/JJ
Armour Pharmaceutical Company Ltd.,
Hampden Park,
Eastbourne,
East Sussex.

September 1981

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ARMOUR000779

ARMO0000091_0002

APPLICATION FOR A PRODUCT AUTHORISATION FOR

F A C T O R A T E

(DOUBLE FILL PRESENTATION)

PART I SUMMARY

1. NAME AND ADDRESS OF APPLICANT

Armour Pharmaceutical Company,
Hampden Park,
Eastbourne,
U.K.

2. NAME AND ADDRESS OF PROPOSED HOLDER OF AUTHORISATION

As in 1. above.

3. NAME AND ADDRESS OF PERSON RESIDENT IN IRELAND

Berk Pharmaceuticals Limited,
Dublin Industrial Estate,
Glasnevin,
Dublin 2.

4. ROLE OF PROPOSED HOLDER OF AUTHORISATION

(a) As person responsible for composition of the product in Ireland.

(b) As person who imports or procures its importation.

5. NAME AND ADDRESS OF ACTUAL IMPORTER

Berk Pharmaceuticals Limited,
Dublin Industrial Estate,
Glasnevin,
Dublin 2.

6. ACTIVITIES FOR WHICH THE AUTHORISATION IS REQUIRED

(a) Selling or supplying the product in Ireland.

(b) Importing or procuring the importation of the product.

7. PROPRIETARY NAME OF THE PRODUCT

FACTORATE (Double Fill)

8. PRODUCT FORM

Vials of lyophilised powder for intravenous injection after reconstitution with Water for Injections B.P.

9. ACTIVE CONSTITUENT

Antihaemophilic Factor (Human).

10. CLINICAL USE

Treatment of Haemophilia A resulting from deficiency of Antihaemophilic Factor (Factor VIII).

11. RECOMMENDED DOSAGE

Dosage should be adjusted according to the patient's individual needs. Generally one unit of Factor VIII activity per kg will increase circulating Factor VIII level by 2%.

The following general doses are suggested:

(1) Overt bleeding Initially 20 units per kg of bodyweight 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 one a day for 2 - 3 days.

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

(c) Haemorrhage 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 - 40 units per kg bodyweight 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.

12. SIDE EFFECTS, CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS

Warnings

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 in this leaflet, 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 point.

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 haematocrit and direct Coombs test for signs of progressive anaemia.

Contra-Indications

There are no known contra-indications to antihaemophilic fraction.

13. METHOD OF RETAIL SALE OR SUPPLY

To hospitals only.

14. METHOD OF SALES PROMOTION

Via the professions as a prescription item.

15. MANUFACTURE OF DOSAGE FORM

Manufacture of the dosage form will be carried out by Armour Pharmaceutical Company, P.O. Box 511, Kankakee, Illinois 60901, U.S.A. Assembly of the product into final containers will be carried out at Armour Pharmaceutical Company Limited, Hampden Park, Eastbourne. Vials of Water for Injections BP supplied in Home Treatment Packs for reconstitution of the product will be supplied by Phoenix Pharmaceuticals, Phoenix Estate, Caerphilly Road, Cardiff, Wales, CF4 4XG.

16. QUALITY CONTROL

Quality control in-process and on the finished product will be exercised by Armour Pharmaceutical Company, Kankakee, USA.

The responsibility for release of the product, based on batch analysis data supplied with each batch, will rest on the Quality Control Manager at Armour Pharmaceutical Company Limited, Eastbourne.

17. CONTAINERS

Factorate (Double Fill) is supplied in 100 ml Type I glass vials with 20 mm neck finish. The closure is a grey butyl rubber stopper with an aluminium seal and blue non-traumatic flip-top cap. Home treatment packs are made available in certain instances and these contain vials of Water for Injections BP for reconstitution of the product.

18. LABELLING

Texts for product label and package insert are attached.

19. SAMPLE OF PACKAGED PRODUCT

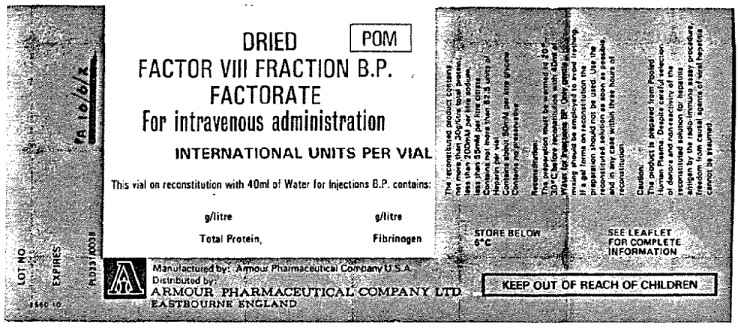
Factorate is supplied in packs of ten vials. A sample vial is provided with this documentation.

20. MANUFACTURING AUTHORISATION

Factorate is manufactured by Armour Pharmaceutical Company Kankakee, in accordance with Establishment Licence 149, issued by the United States Department of Health, Education and Welfare. A copy of this document is attached.

21. OTHER MARKETING AUTHORISATIONS

Factorate, single and double fill, are licensed for sale in the United Kingdom under Product Licence No. 0231/0038 granted in March 1976. The single-fill presentation of Factorate is registered in Eire under Product Authorisation No. 10/6/1, granted in May 1977.



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administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation (Dormandy 1977).

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 on page 3, 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.

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 haematocrit and direct Coombs test for signs of progressive anaemia.

CONTRAINDICATIONS

There are no known contraindications to antihaemophilic fraction.

STORAGE

FACTORATE is to be stored below 6°C.
When stored as directed, it will maintain its labelled potency for the period indicated on the label.

HOW SUPPLIED

FACTORATE is supplied in single dose vials (potency is stated on each vial label).

REFERENCES

1. Abildgaard. "Current Concepts in the Management of Hemophilia". From "Current Problems in Pediatric Hematology" (Ed. Oski, Jaffe and Miescher). Grune and Stratton, 1975.
2. Abildgaard et al. "Treatment of Hemophilia with Glycine-Precipitated Factor VIII" *N. Engl. J. Med.*, 1968, 275, 471.
3. Bangham, Biggs et al. "A Biological Standard for Measurement of Blood Coagulation Factor VIII Activity". *Bull. Wld. Hlth. Org.*, 1971, 45, 337.
4. Biggs et al. "Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia based on Studies made During 1969-1972". *Brit. J. Haematol.*, 1974, 27, 391.
5. Brinkhous et al. "A New High-Potency Glycine-Precipitated Antihaemophilic Factor (AHF) Concentrate". *J. Amer. Med. Ass.*, 1968, 205, 613.
6. Britton, Harrison and Abildgaard. "Early Treatment of Hemophilic Hemarthroses with Minimal Dose of New Factor VIII Concentrate". *J. Pediat.*, 1974, 85, 245.
7. Dormandy. "Haemophilia A and B". *Prescribers J.*, 1977, 17, 8.
8. Georgia and Breckenridge. "The use of Factor VIII and Factor IX Concentrates During Surgery". *J. Amer. Med. Ass.*, 1970, 214, 1673.
9. Mazza et al. "Antihemophilic Factor VIII in Hemophilia: Use of Concentrates to Permit Major Surgery". *J. Amer. Med. Ass.*, 1970, 211, 1818.
10. Rizza. "Clinical Management of Haemophilia". *Br. Med. Bull.* 1977, 3, 225-230.

Manufactured by Armour Pharmaceutical Company, USA

Distributed by

Armour Pharmaceutical Company Limited, Eastbourne, England.

Revised July 1980 PL 0231/0038

1693-10

To the Medical and Pharmaceutical Professions only.

Dried Human Antihaemophilic Fraction Sterile B.P.

FACTORATE

(Double Fill)

Armour Pharmaceutical Company Limited Eastbourne, England

DRIED HUMAN ANTIHAEMOPHILIC FRACTION STERILE FACTORATE FOR INTRAVENOUS USE

Dried Human Antihaemophilic Fraction FACTORATE is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma intended for use in therapy of classical haemophilia (Haemophilia A).

A hereditary disorder of blood coagulation occurring almost exclusively in males, Haemophilia A 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 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 transfusions, cryoprecipitate or by injections of Factor VIII concentrates. Obvious advantages of the use of concentrates of Factor VIII are the avoidance of hyperproteinaemia, 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 I of Cohn to highly purified, potent preparations. Dried Human Antihaemophilic Fraction-FACTORATE is in an intermediate category, being a purified cryoglobulin complying with the standards of the B.P.

COMPOSITION AND STANDARDISATION

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 Sterile Water for Injections B.P. is added as directed.

RECOMMENDED RECONSTITUTION

Reconstitute FACTORATE using 40 ml Sterile Water for Injections B.P. using standard aseptic precautions.

Warm both diluent and FACTORATE 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 Injection

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 suitable intravenous needle.
3. Administer solution by slow intravenous injection (40 ml in 5-10 minutes).

Intravenous Infusion

The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2403: 1982, Transfusion Equipment for Medical Use.

1. Prepare solution of FACTORATE 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 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.

DOSAGE

FACTORATE 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, 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 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 postoperatively is suggested.
5. **Dental Extractions**—For simple extractions a preoperative dose of 20-25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C.

ESTABLISHMENT LICENSE

FOR THE MANUFACTURE OF
BIOLOGICAL PRODUCTS

This is to certify that Establishment License No. 149 is hereby issued to Armour Pharmaceutical Company, the manufacturer, located at Kankakee, Illinois, through the establishment identified as Armour Pharmaceutical Company, located at Kankakee, Illinois,

pursuant to Section 351 of the Public Health Service Act, approved July 1, 1944 (58 Stat. 702, 42 U.S.C. 262), as amended, and the regulations thereunder. The license authorizes the manufacturer to maintain an establishment for the propagation or manufacture and preparation for sale, barter, or exchange in the District of Columbia, or for sending, carrying, or bringing for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives, for which the manufacturer holds an unsuspended and unrevoked product license issued by the Secretary of Health, Education, and Welfare pursuant to said Act and regulations.

Date JAN 05 1979

GRO-C

Director, Bureau of Biologics
Food and Drug Administration

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