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LP2

REGISTRATION
14 JUN 1979

Mr S G Brooks
Armour Pharmaceutical Co Ltd
Hampden Park
Eastbourne
Sussex BN22 9AG

Your reference SGH/JH

Our reference PL/0231/0044

Date 13 June 1979

Dear Sir

MEDICINES ACT 1968: PART II LICENSING

In accordance with the provisions of Product Licence number 0231/0044, the licensing authority hereby:

i. requests that samples (4 vials of finished product) together with full protocols of the tests which have been applied to each batch of High Potency Factorate, and also a sample of the proposed label, be sent to Dr Duncan Thomas at the National Institute for Biological Standards and Control, Holly Hill, Hampstead, London NW3 6RB;

ii. directs that no such batch be sold or offered for sale until a certificate authorising the sale has been issued by the licensing authority.

Yours faithfully

GRO-C

(Miss) B A Leigh

DRAFT PACKAGE INSERT

Dried Human Antihaemophilic Fraction Sterile

HIGH POTENCY FACTORATE

Armour Pharmaceutical
Company Limited
Eastbourne, England

DRIED HUMAN ANTIHAEMOPHILIC FRACTION STERILE FACTORATE

FOR INTRAVENOUS USE

Dried Human Antihaemophilic Fraction HIGH POTENCY 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 corrections 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. HIGH POTENCY FACTORATE is a purified cryoglobulin with much of the fibrinogen, as well as other plasma proteins, removed. Upon reconstitution, as directed, HIGH POTENCY FACTORATE contains 20 to 40 times as much Factor VIII as does an equal volume of plasma. Thus it may be used to correct deficiencies in Factor VIII levels without overloading the circulatory system.

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 sodium chloride (approximately 20 to 40 mg per 100 International Units). When prepared for administration as directed under reconstitution, the resulting solution will have approximately twice the tonicity of isotonic saline.

RECOMMENDED RECONSTITUTION

Reconstitute HIGH POTENCY FACTORATE using 30 ml sterile Water for Injections B.P. using standard aseptic precautions.

Warm both diluent and HIGH POTENCY FACTORATE at from 20°C to 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 10 to 15 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used.

ADMINISTRATION

Standard asceptic 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, 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 section 3 or 4 of British Standard 2463: 1962, Transfusion Equipment for Medical Use.

1. Prepare solution of HIGH POTENCY 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 HIGH POTENCY 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

HIGH POTENCY 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 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 preoperative dose of 20 - 25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of epsilon aminocaproic 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

HIGH POTENCY FACTORATE is to be stored below 6^{o}C.

When stored as directed, it will maintain its labelled potency for the dating period indicated on the label.

HOW SUPPLIED

HIGH POTENCY FACTORATE is supplied in single dose vials.

Potency is stated on each 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.*, 1966, 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. Haemotol.*, 1974, 27, 391.

5. Brinkhous et al. "A New High-Potency Glycine-Precipitated Antihemophilic 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. George 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. Walsh et al. "The Therapeutic Role of Epsilon-Aminocaproic Acid (EACA) for Dental Extraction in Hemophiliacs". *Annals N.Y. Acad. Sci.*, 1975, 240, 267.

Manufactured by Armour Pharmaceutical Company , USA

Distributed by

Armour Pharmaceutical Company Limited,
Eastbourne, England.

PL 0231/

LOT NO .....

EXPIRES .....

PL0231/.....

DRIED HUMAN ANTIHAEMOPHILIC FRACTION STERILE
HIGH POTENCY FACTORATE®

POM

For Intravenous Administration

INTERNATIONAL UNITS PER VIAL

This vial on reconstitution with 30ml of Sterile Water for Injections B.P. contains g/litre Total Protein, g/litre Fibrinogen

STORE BELOW 6°C

SEE LEAFLET FOR COMPLETE INFORMATION

Manufactured by Armour Pharmaceutical Company U.S.A.
Distributed by
ARMOUR PHARMACEUTICAL COMPANY LTD.
EASTBOURNE ENGLAND

When reconstituted with 30 ml. of Sterile Water for Injections B.P. the contents of this vial are approximately two times isotonic.
Contains not more than 30 units of Heparin per vial.
Contains Glycine USP.
Contains no preservative.

Reconstitution:

The preparation must be warmed to 20°–25° C before reconstitution with 30ml of Sterile Water for Injections BP. Only gentle mixing should be employed to avoid frothing. If a gel forms on reconstitution the preparation should not be used. Use the reconstituted solution as soon as possible and in any case within three hours of reconstitution.

Caution:

The product is prepared from Pooled Human Plasma. Despite careful selection of donors and non-reactivity of the reconstituted solution for hepatitis B antigen by the radio-immuno assay procedure, freedom from causal agents of viral hepatitis cannot be assumed.

KEEP OUT OF REACH OF CHILDREN

PRODUCT LICENCES - REQUIREMENTS AS TO REPORTING SUSPECTED ADVERSE REACTIONS

1. Para 4 of the standard provisions for product licences, Schedule 1 to the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 read as follows:-

"The licence holder shall maintain a record of reports of which he is aware of adverse effects in one or more human beings or animals associated in those reports with the use of any medicinal product to which the licence relates, which shall be open to inspection by a person authorised by the licensing authority, who may take copies thereof, and if the licensing authority so directs, the licence holder shall furnish the licensing authority with a copy of any such reports of which he has a record or of which he is or subsequently becomes aware."

2. In the case of new products a direction will be made requiring all suspected reactions originating in the United Kingdom to be reported until further notice. For all other products the direction will relate only to serious or unexpected reactions. (The direction will also require relevant information from abroad to be reported, but not in the form of copies of individual reports, and only if that information suggests a potentially important hazard may exist.)

3. In either case action is required only in respect of reports to the holder of the licence made or confirmed by medical or dental practitioners, pharmacists, coroners or procurators fiscal. (The standard provision requires a record to be kept of other reports and for this record to be kept available for inspection.)

4. Reports sent direct to the Committee should be addressed to the Medical Assessor, Committee on Safety of Medicines, Finsbury Square House, 33/37A Finsbury Square, London EC2A 1PP. Reports falling within the terms of the direction should be forwarded without delay to the licensing authority for the information of the Committee. Where a report comes from a source other than the patient's own doctor, it will sometimes be appropriate first to check the report with him.

5. It will be convenient for reports to be in the same form as the yellow report cards supplied to practitioners, and copies of a form for this purpose are enclosed. Where more complete reports are available, however, a full copy should be sent.

6. If the practitioner concerned is known to have completed a yellow card in respect of a particular report, it will be sufficient for the holder of the licence to supply an appropriate reference to this report (quoting the name of the practitioner, the date of the report and the product concerned).

7. The following are examples of reactions which should always be regarded as serious and should therefore be reported in all cases:-

Anaphylaxis	Severe CNS effects
Blood dyscrasias	Severe skin reactions after injection or topical application.
Congenital abnormalities	Reactions in pregnant women.
Endocrine disturbances	Unexplained lack of effect or paradoxical effects:
Fertility effects	eg. possibility of reduction in efficacy
Haemorrhage from any site	due to drug-interaction, or hypertension
Jaundice, however mild	with a hypotensive agent.
Ophthalmic signs or symptoms	

Any symptom of a serious or life-threatening disease which was not present before the patient was treated with the drug and any significant worsening of a concurrent condition not regarded as an indication for treatment with the drug in question.

(Standard Direction)

(Human Medicines)

MEDICINES ACT 1968

DIRECTION AS TO REPORTING OF SUSPECTED ADVERSE REACTIONS

Holder of the Licence Armour Pharmaceutical Company Ltd : PL/0231/0044.

1. In pursuance of para 4 of Part I of Schedule 1 to the Medicines Act (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No. 972) as applied to any product licence held by the holder of the licence named above, the licensing authority directs the holder of the licence to furnish to the authority for the information of the Committee on Safety of Medicines, except where the holder of the licence has already furnished the Committee with the information and received an acknowledgement, copies of all reports, as defined in 2 below and originating in the United Kingdom, of which he is aware of adverse effects on human beings suspected of association with the use of any medicinal product to which any such licence relates. The holder of the licence is required to furnish such reports as soon as possible after receipt or, where appropriate, immediately after substantiation by the patient's doctor. Licence holders should ensure that in all cases such reports are furnished not later than one month after receipt.

2. This direction applies to any report made by or confirmed by a medical or dental practitioner, a pharmacist, a coroner or a procurator fiscal and which relates to an adverse effect which has occurred at doses in normal use and falls within one or more of the following categories:-

a. a reaction with a fatal outcome,

b. a reaction of sufficient severity to interfere with normal activities,

c. any unusual reaction, not referred to in standard publication or in literature issued by the manufacturer or licence holder,

d. any reaction which may be an example of possible drug-interaction.

3. The holder of the licence is also required similarly to furnish without delay information from abroad of which he becomes aware about suspected adverse reactions to medicinal products of the kind to which the licence relates, that is containing the same active ingredients, which suggests that an associated serious hazard may exist. Separate reports of every relevant individual suspected adverse effect occurring abroad coming to the notice of the holder of the licence are, however, not required.

4. This direction is without prejudice to any specific direction made in connection with a particular product and remains in force until withdrawn or amended by a fresh notification in writing by the licensing authority.

CSM/AR/IND

IN CONFIDENCE - REPORT ON SUSPECTED TOXICITY OR SIDE-EFFECTS

NOTES FOR GUIDANCE

1. For all drugs, please record serious or unusual reactions. For new drugs record all reactions.
2. Record, on the top line, the drug suspected of causing harmful effects to the patient at normal dosage.
3. Record all other drugs, including self-medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Please do not be deterred from reporting because some details are not known.

Name of Patient: (Required in confidence to allow linkage with other reports for same patient)	From (Name and address): Company doctor or other representative of product licence holder - Signed: Date:

Sex	Age or Date of Birth	Weight if known	Name of patient's own doctor (and address if known):

DRUGS*(Brand name where appropriate)	ROUTE	DOSE	DATES From	DATES To	INDICATIONS
.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
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.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....
(*For Vaccines give Batch No.)					

REACTIONS (List separately)	Started	Ended	OUTCOME (e.g. fatal: recovered)
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

Additional Notes