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Letter acknowledged by DHSS. 24/5/76
(Mrs. A. Smith.

Armour Pharmaceutical Company Limited

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17th May 1976

Mr. E.J. Nicholas,
Department of Health & Social Security,
Medicines Division,
Finsbury Square House,
33-37A Finsbury Square,
London. EC2A 1PP.

Dear Mr. Nicholas,

Product Licence No. 0231/0038

Thank you for the formal documents in respect of the above product licence forwarded with your letter of 7th May 1976. As discussed by telephone with your department, I have now been informed that the active constituent is manufactured only at Armour Pharmaceutical Co., P.O. Box 511, Kankakee, Illinois 60901, U.S.A., and not Metrix Clinical and Diagnostics Division. The previous temporary arrangement with Metrix has now been terminated.

I would be obliged therefore if the attached documents could delete the involvement of the Metrix Division at item 7 of the Schedule. I have amended page 3 of the supplementary particulars in my original submission and I enclose a copy of this for replacement in the documents held by you.

This change means that only Kankakee are the manufacturer of the active constituent and the dosage form. My letter of declaration under Section 19(3) Medicines Act 1968 which gives permission for the premises to be inspected, was forwarded on 4th June 1975.

The data sheet for Factorate are now in draft form and I enclose a copy for your attention.

Yours faithfully,
ARMOUR PHARMACEUTICAL COMPANY LTD.

S.G. Brooks B.Sc.,
Head of Regulatory Affairs.

ENCL.

PRODUCT LICENCE NUMBER
P.L. 0231/0038

PRODUCT LICENCE HOLDER
Armour Pharmaceutical Company Ltd
Hampden Park, Eastbourne, Sussex, BN22 9AG
April 1976 F/DS63/6

FACTORATE

DATA SHEET

PRESENTATION

Dried Human Antihæmophilic Fraction FACTORATE is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma.
Upon reconstitution, Dried Human Antihæmophilic Fraction – FACTORATE contains 5 to 10 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.
Each vial contains the labelled amount of antihæmophilic activity in International Units (One International Unit is the activity equivalent to the average Factor VIII content of 1 ml aliquot of 167 samples of fresh normal plasma, as determined in an international collaborative study).
Each vial also contains sufficent sodium chloride to make the reconstituted solution approximately isotonic when sterile Water for Injections B.P., 25 ml, is added.

USES

For use in therapy of classic hæmophilia (Hæmophilia A).

DOSAGE

FACTORATE is for intravenous administration only. Although dosage must be adjusted according to the needs of the patient (weight, severity of hæmorrhage, 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 twenty-four hours and the same dose every twelve hours for 3 to 4 days.

2. Muscle hæmorrhages

(a) Minor hæmorrhages in extremities or non-vital areas: 10 units per kg. once a day for 2 or 3 days.
(b) Massive hæmorrhages in non-vital areas: 10 units per kg. by infusion at 12-hour intervals for two days and then once a day for two more days.
(c) Hæmorrhages near vital organs (neck, throat, sub-peritones) 20 units per kg. initially; then 10 units per kg. every eight hours. After two days the dose may be reduced by one-half.

3. Joint hæmorrhages

10 units per kg. every eight hours for a day; then twice daily for one or two days. If aspiration is carried out, 10 units per kg. just prior to aspiration with additional infusions of 10 units per kg. eight hours later and again on the following day.

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4. Surgery

Dosages of 30 to 40 units per kg. body weight prior to surgery are recommended. After surgery 20 units per kg. every eight hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40 per cent of normal for at least ten days post-operatively is suggested. As a general rule one unit of Factor VIII activity per kg. will increase by 2 per cent the circulating Factor VIII level. Adequacy of treatment must be judged by the clinical effects – thus the dosage may vary with individual cases.

ADMINISTRATION

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. Using aseptic technique, attach a filter needle to a sterile disposable syringe (10 ml. or 25 ml.). 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 infusion set or intravenous needle. Administration equipment should comply with that described in section 3 or 4 of British Standard 2463: 1962, Transfusion Equipment for Medical Use.
3. Administer solution intravenously at a rate comfortable for the patient. Usually 25 ml. may be given in about five minutes.

Intravenous infusion

1. Prepare solution of FACTORATE as recommended under Reconstitution.
2. Slip the vial into the plastic suspension sleeve. Keep vial upright.
3. Follow the Directions for Use accompanying the intravenous Administration Set (see Administration, 2).
4. If more than one vial is to be administered to the same patient, the administration set may be transferred to a second vial prepared according to steps 1 and 2 above.
5. When infusion of FACTORATE is complete, the administration set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.
6. After use, discard administration set, needles and vials together with any unused solution.

Recommended reconstitution

Reconstitute FACTORATE using 25 ml. sterile Water for Injections B.P. using standard aseptic precautions.

Warm both diluent and FACTORATE at from 20°C to 25°C. 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.

WARNINGS

Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HB_sAg) 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 antihæmophilic fraction.

PRECAUTIONS

Factor VIII contains low levels of group A and B isohæmagglutinins. When large volumes are given to patients of blood groups A, B or AB the possibility of intravascular hæmolysis should be considered.

PHARMACEUTICAL PRECAUTIONS

FACTORATE is to be stored at refrigerator temperature (2°C–6°C).

LEGAL CATEGORY

T.S.A.

PACKAGE QUANTITIES

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

FURTHER INFORMATION

A hereditary disorder of blood coagulation occurring almost exlusively in males, hæmophilia 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, anti-hæmophilic factor. Factor VIII provides temporary replacement of the missing clotting factor.

Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals must be preceded by temporary corrections of the clotting abnormality with fresh plasma transfusions, or by injections of Factor VIII concentrates. Obvious advantages of the use of concentrates of Factor VIII over plasma are the avoidance of hyper-proteinemia and possible kidney dysfunction 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 Antihæmophilic Fraction – Factor VIII is in an intermediate category, being a purified cryoglobulin with much of the fibrinogen, as well as other plasma proteins, removed. When stored as directed it will maintain its labelled potency for the dating period indicated on the label.

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