DHSS - HP Factorate

Armour Pharmaceutical Company Limited

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SJH/JJ

13th February, 1985

Dr. J. Purves,
Department of Health and Social Security,
Medicines Division,
Market Towers,
1 Nine Elms Lane,
Vauxhall,
LONDON,
SW8 5NQ

Dear Dr. Purves,

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

Further to your conversation with Mr. Collins we enclose label texts for the above products. These labels will also carry the appropriate Product Licence numbers.

Please do not hesitate to contact us should you require further information.

Yours sincerely,

GRO-C

S. J. HINCE
Assistant Regulatory Affairs Manager

IMPORTANT: SEE LEAFLET FOR COMPLETE INFORMATION

RECONSTITUTION: Reconstitute in 30ml Sterile Water for Injection. Warm both Diluent and Factorate to between 20°C and 30°C. Direct Diluent down side of vial, gently rotate until contents are dissolved. **DO NOT SHAKE VIAL.** Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes less than five minutes. Discard if a gel forms on reconstitution. Use solution within three hours of reconstitution.

CAUTION: This solution is of human origin, despite careful selection of donors and processing, it cannot be assumed to be free of hepatitis virus.

21838-10

DRIED FACTOR VIII FRACTION FACTORATE

For intravenous administration

HEAT TREATED

Store between 2°C and 6°C

manufactured by:
ARMOUR PHARMACEUTICAL COMPANY, U.S.A.
Distributed by:
ARMOUR PHARMACEUTICAL COMPANY LTD
EASTBOURNE · ENGLAND

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:

g/litre total protein

g/litre fibrinogen

Approx electrolyte concentration
Sodium 250 mM per litre
Citrate 40 mM per litre
Contains about 100 mM per litre Glycine
Contains no preservative

The reconstituted product contains not more than 30g per litre total protein; less than 200mM per litre sodium; less than 55mM per litre citrate. Contains not more than 62.5 units of heparin per vial.
Contains about 50mM per litre glycine. Contains no preservative.

Reconstitution:
The preparation must be warmed to 20° to 30°C before reconstitution. Reconstitute Factorate with Water for Injections B.P. using standard aseptic precautions. Reconstitution with 20ml Water for injections B.P. will give a solution which complies with the B.P. In some circumstances, where a small volume is required, it may be preferable to reconstitute Factorate with 10ml of Water for Injections, B.P.; however the content of sodium and citrate ions will not comply with the B.P. 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.

DRIED FACTOR VIII FRACTION B.P. FACTORATE

POM

For intravenous administration

HEAT TREATED

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

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:

g/litre total protein

g/litre fibrinogen

when reconstituted with 20ml Water for Injections B.P.

Keep all medicines out of the reach of children

21800-10

The reconstituted product contains not more than 30g per litre total protein; less than 200mM per litre sodium; less than 55mM per litre citrate. Contains not more than 62.5 units of heparin per vial.
Contains about 50mM per litre glycine. Contains no preservative.

Reconstitution:
The preparation must be warmed to 20° to 30°C before reconstitution. Reconstitute Factorate with Water for Injections B.P. using standard aseptic precautions. Reconstitution with 40ml Water for Injections B.P. will give a solution which complies with the B.P. In some circumstances, where a small volume is required, it may be preferable to reconstitute Factorate with 20ml of Water for Injections, B.P.; however the content of sodium and citrate ions will not comply with the B.P. 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 antigen by the radio-immuno assay procedure, freedom from causal agents of viral hepatitis cannot be assumed.

DRIED FACTOR VIII FRACTION B.P. FACTORATE

POM

For intravenous administration

HEAT TREATED

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

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:
g/litre total protein
g/litre fibrinogen

when reconstituted with 40ml Water for Injections B.P.

Keep all medicines out of the reach of children

21802-10

The reconstituted product contains not more than 30g per litre total protein; less than 200mM per litre sodium; less than 55mM per litre citrate. Contains not more than 62.5 units of heparin per vial.
Contains about 50mM per litre glycine. Contains no preservative.

Reconstitution:
The preparation must be warmed to 20° to 30°C before reconstitution. Reconstitute Factorate with Water for Injections B.P. using standard aseptic precautions. Reconstitution with 60ml Water for Injections B.P. will give a solution which complies with the B.P. In some circumstances, where a small volume is required, it may be preferable to reconstitute Factorate with 30ml of Water for Injections, B.P.; however the content of sodium and citrate ions will not comply with the B.P. 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 antigen by the radio-Immuno assay procedure, freedom from causal agents of viral hepatitis cannot be assumed.

DRIED FACTOR VIII FRACTION B.P. FACTORATE

POM

For intravenous administration

HEAT TREATED

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

FOR NAMED PATIENT SUPPLY

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:
g/litre total protein
g/litre fibrinogen

when reconstituted with 60ml Water for Injections B.P.

Keep all medicines out of the reach of children

21804-10

IMPORTANT: SEE LEAFLET FOR COMPLETE INFORMATION

RECONSTITUTION: Reconstitute in 10ml Sterile Water for Injection. Warm both Diluent and Factorate to between 20°C and 30°C. Direct Diluent down side of vial, gently rotate until contents are dissolved. **DO NOT SHAKE VIAL.** Vigorous shaking will cause frothing and prolong reconstitution time. Complete solution ily takes less than five minutes. Discard if a gel forms on reconstitution. Use solution within three hours of reconstitution.

CAUTION: This solution is of human origin, despite careful selection of donors and processing, it cannot be assumed to be free of hepatitis virus.

21832-10

DRIED FACTOR VIII FRACTION FACTORATE

For intravenous administration

HEAT TREATED

Store between 2°C and 6°C

manufactured by:
ARMOUR PHARMACEUTICAL COMPANY, U.S.A.
Distributed by:
ARMOUR PHARMACEUTICAL COMPANY LTD
EASTBOURNE · ENGLAND

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:
g/litre total protein
g/litre fibrinogen

Approx electrolyte concentration
Sodium 250 mM per litre
Citrate 40 mM per litre
Contains about 100 mM per litre Glycine
Contains no preservative

When reconstituted with 20ml Water for Injections, B.P., the contents of this vial are approximately isotonic, and contain not more than 200mM per litre sodium and not more than 55mM per litre citrate. Contains not more than 30 units of heparin per vial. Contains about 50 mM per litre glycine. Contains no preservative.

RECONSTITUTION:
The preparation must be warmed to 20° – 30°C before reconstitution with 20ml of Water for Injections, B.P. 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.

DRIED HUMAN ANTIHAEMOPHILIC FRACTION B.P. (STERILE) POM

HIGH POTENCY FACTORATE

For intravenous administration

HEAT TREATED

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

LOT:

EXPIRES:

I.U. PER VIAL

This vial contains:
g/litre total protein
g/litre fibrinogen

when reconstituted with 20ml Water for Injections B.P.

Keep all medicines out of the reach of children

21822-10

PROPOSED DATA SHEET TEXT

HIGH POTENCY FACTORATE

PRESENTATION

Dried Human Antihaemophilic Fraction High Potency Factorate is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma. It conforms to the monograph for dried Human Antihaemophilic Factor BP.

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 nomral 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.

USES

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

DOSAGE AND ADMINISTRATION

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 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 High Potency Factorate 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	10
500	20
1000	30
2000	60

Warm both diluent and High Potency Factorate 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 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.

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 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 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 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 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