IMMUNO

AKTIENGESELLSCHAFT FÜR CHEMISCH-MEDIZINISCHE PRODUKTE

PRODUKTIONSBETRIEBE:
ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES. M. B. H. IMMUNO DIAGNOSTIKA GES. M. B. H.

IMMUNO LTD.

Att. Mr. Nicholson

Arctic House,
Rye Lane,
Dunton Green, Nr. Sevenoaks
KENT TN14 5HB
G r e a t B r i t a i n

INDUSTRIESTRASSE 72
A-1220 WIEN

TELEFON: (0222) 2300-0 (Zentrale)
23 55 45/DW . . .
TELEGRAMME: IMMUNO WIEN
TELEX: 132722 imuno a
134865 imuno a

Vienna, Jan. 22, 1985
1610/Hb

Re: KRYOBULIN TIM 2

Dear Mr. Nicholson,

Attached please find the pack inserts for Kryobulin Tim 2 which you requested yesterday.

Sincerely yours,
IMMUNO AG

GRO-C

Dipl.Dolm. I. Diernhofer
Licensing Department

Enclosure

PACKS

1 R/C bottle containing lyophilised KRYOBULIN TIM 2. The Factor VIII activity is stated on the label of each bottle.

1 R/C bottle containing Water for Injections B.P. (10 ml, 20 ml or 50 ml) according to Factor VIII activity.

1 Kit for reconstitution and filtration. Certain packs also contain injection equipment.

REFERENCES

1. BIGGS, R.; MACFARLANE, R.G.: Treatment of Haemophilia and other Coagulation Disorders. 1 Ed. Blackwell Scientific Publications, Oxford (1966)
2. BIGGS R., RUSH B.M., MACFARLANE R.G., MATTHEWS J.M., JOHNSTONE F.C., HAYTON-WILLIAMS D.S.: Further Experience in Use of Human Antihaemophilic Globulin (H.A.H.G.) for Control of Bleeding after Dental Extraction in Haemophilic Patients. Lancet 1, 969 (1965)
3. BOWIE, J.W.; DIDISHEIM P.; THOMPSON J.J.; OWEN C.A.: The Spectrum of von Willebrand's Disease. Thrombos.Diathes.haemorrh. 18, 40 (1967)
4. BRINKHOUS K.M.: The Haemophilias: International Symposium. Washington. The University of North Carolina press, Chapel Hill (1964)
5. DEUTSCH E.: Haemorrhagische Diathesen. Lehrbuch der inneren Medizin, hrsg. R. Gross und D. Jahn, Schattauer Verlag, Stuttgart, S.214 (1966)
6. EIBL H.; FISCHER M.; KUHBÖCK J.: Pseudotumor des Darmbeines bei Haemophilie A. Dtsch.med.Wschr. 90, 1864 (1965)
7. EGLI H.: Blut, Plasma, Serum und Fraktionen. Thrombos. Diathes. haemorrh. Suppl. 19, 45 (1966)
8. EGLI H.: Transfusionstherapie der Haemophilie A und B, Bibl. haemat. Vol. 27, S. 204, Karger Verlag, Basel — New York (1967)
9. FISCHER M.: Die Blutererkrankung. Wien.med. Wschr. 118, 110 (1968)
10. FISCHER M.; DEUTSCH E.: Therapie der Haemophilien. Dtsch. med. J. 19, 499 (1968)
11. FISCHER M.; IRSIGLER K.; LECHNER K.: Internistische Probleme bei haemorrhagischen Diathesen im Zusammenhang mit chirurgischen Eingriffen. Wien. klin. Wschr. 77, 862 (1965)
12. FISCHER M., KRENN J., LECHNER K., STEINBEREITHNER K., VONKILCH, E.: Die Bedeutung der Plasmapherese während der intensiven, postoperativen Behandlung bei Haemophilie. Anaesthesist 17, 72 (1968)
13. GAERISCH F., MEY U.: Prophylaktische Behandlung schwerer Verlaufsformen von Haemophilie A mit Fraktion I (AHG) und PAMBA. Bibl. haemat. Vol. 27, S. 270 Karger Verlag, Basel — New York (1967)
14. KURME A., OTTE, P., LANDBECK G.: Therapie der Folgezustände rezidivierender Gelenksblutungen in Haemophilie. XI. Hamburger Symposium über Blutgerinnung. Schattauer Verlag, Stuttgart — New York S.117 (1969);
15. LANDBECK G., KURME A.: Die Haemophile Kniegelenksarthropathie. Monatsschrift für Kinderheilkunde 118, 29 (1970)
16. LANDBECK G.: Häufigkeit und Schweregrad der Haemophilie — Entwicklung der Blutungssymptomatik. XI. Hamburger Symposium über Blutgerinnung. Schattauer Verlag, Stuttgart — New York S.27 (1969)
17. LANDBECK G.: Substitutionstherapie mit Faktor VIII, und IX Präparaten. 12. Kongr. Deutsche Ges. Haemat. Berlin (1966); H. Pettenkofer: Gezielte Therapie mit Blutbestandteilen. Lehmanns Verlag, München (1968)
18. LANDBECK G.: Blutungskrankheiten mit Mangel an Faktor VIII. IV. Hamburger Symposium über Blutgerinnung (1961). Thrombos. Diathes. haemorrh. Suppl. 2 ad Vol. 6, 60 (1962)
19. LANDBECK G.: Über die Behandlung der Haemophilie. Med Welt (1960)
20. LECHNER K.: Immunologisch bedingte Koagulopathien. Thrombos. Diathes. haemorrh. Suppl. 34, 33 (1969)
21. MARGOLIUS A.J., et al.: Circulating Anticoagulants: A study of 40 Cases and a Review of the Literatur. Medicine 40, 145 (1961)
22. NILSSON I.M., BLOMBÄCK M., THILEN A., FRANCKEN I.V.: Carriers of Haemophilia A-A laboratory study. Acta Med. Scand. 165, 357 (1959)
23. NILSSON I.M., BLOMBÄCK M., RAMGREN O.: Haemophilia in Sweden. Acta Med. Scand. 170, 665 (1961)
24. BLOMBÄCK M., NILSSON I.M.: Treatment of Haemophilia A with Human Antihaemophilic Globulin. Acta med. Scand. 161, 301 (1958)
25. POLLER L.: Recent Advances in Blood Coagulation. Churchill London (1969)
26. POOL J.G., HERSHGOLD E.J., PAPPENHAGEN R.: High-potency Antihaemophilic Factor Concentrate prepared from Cryoglobulin Precipitate. Nature (London) 203, 312 (1964)
27. POOL J.G., SHANNON A.E.: Production of High-potency Concentrates of Antihaemophilic Globulin in a Closed Bag System. New Engl. J. Med. 273, 1443 (1965)
28. RATTNOFF O.D.: Treatment of haemorrhagic disorders. Hoeber, New York (1968)
29. RIZZA C.R.: The Management of Haemophilia. Practitioner 20, 763 (1970)
30. VALDERRAMA J.A., MATTHEWS J.M.: The Haemophilic Pseudotumor, or Haemophilic Subperiosteal Haematoma. J. Bone & Joint Surg. 47 B, 256 (1965)
31. SCHIMPF K., FISCHER B., ROTHMANN P.: Die ambulante Dauerbehandlung der Hämophilie A und der Hämophilie B. Eine kontrollierte Studie. Welthaemophiliekongreß Helsinki 75
32. DORMANDY K.M., TAMAGNINI G.P., ELLIS D., MAYCOCK W.D.A.: Factor VIII Concentrate in Haemophilia. The Lancet, 188 (1975)
33. TOPLEY E., et al: The relation of the isoagglutinins in pooled plasma to the haemolytic anaemia of burns. J. clin. Path. 16, 79 (1963)
34. MOLLISON P.L.: Blood Transfusion in Clinical Medicine. Fourth Edition 1967
35. OBERMANN H.A. et al.: Erythrocyte Sensitization and Anemia due to Isoantibodies in Lyophilized Pooled Plasma. JAMA Vol. 198, No. 3, 323 (1966)
36. RUTZKY J. et al.: Anti-A Agglutinins in Pooled Plasma as a Cause of Haemolytic Anemia. J. of Hematology No. 5, (1956)
37. DARNBOROUGH J.: The anti-A and anti-B antibody content of pooled plasma. J. Clin. Path. 16, 74 (1963)
38. MARDER V.J. et al.: Major Surgery in Classic Hemophilia using Fraction I. Am. J. of Med. Vol. 41 (1966)

Distributed by
IMMUNO LTD
Arctic House, Rye Lane, Dunton Green,
Nr. Sevenoaks, Kent TN14 5HB
Tel.: Sevenoaks (0732) 458101

Manufactured by
ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE GES.M.B.H.
Production Division of
IMMUNO AG Vienna Austria

6209221EA24/133cd

Kryobulin® TIM 2
Dried Factor VIII Fraction B.P. heat-treated

P.O.M.

MANUFACTURE AND COMPOSITION

KRYOBULIN TIM 2 is rich in clotting Factor VIII and is in a purified, concentrated and stabilised form. The lyophilised product is standardised in terms of international units of Factor VIII*. It may be stored for two years if storage conditions are observed.
KRYOBULIN TIM 2 is prepared from the pooled plasma of suitable** human donors.
To decrease the potential risk of transmission of viral infections the following steps are taken:

1. Donor and Plasma Selection:
   All donations and pools of plasma used in the manufacture of KRYOBULIN TIM 2 and the final product were tested for HB_S-antigen by Radio Immune Assay (RIA) and found non-reactive.
2. Thermoinactivation by Method TIM 2:
   KRYOBULIN TIM 2 is subjected to a model virus controlled product specific thermoinactivation.

INDICATIONS

Prophylaxis and treatment in all cases of inherited or acquired Factor VIII deficiency disorders
- Haemophilia A
- von Willebrand's disease
- On occasions when it is essential that Factor VIII be administered and Factor VIII inhibitors are known to be present in the patient.

Haemorrhages, caused entirely by Factor VIII deficiency and not by other plasmatic or thrombocytic disorders, can be arrested with adequate quantities of KRYOBULIN TIM 2. Under controlled treatment with KRYOBULIN TIM 2, major surgery (abdominal and orthopaedic surgery) may be performed even in patients with severe haemophilia and a Factor VIII concentration of less than 1%.
According to latest reports, the isoagglutinins contained in KRYOBULIN TIM 2 may have a haemolytic effect upon the patient's erythrocytes if large quantities of the preparation are required as e.g. in surgical interventions or in cases of haemophilia accompanied by a circulating Factor VIII inhibitor. In such cases, administration of blood group compatible KRYOBULIN TIM 2 is recommended (i.e. KRYOBULIN TIM 2 obtained exclusively from donors of the same blood group).

DIRECTIONS FOR RECONSTITUTION OF A SOLUTION FOR INJECTION

The lyophilised KRYOBULIN TIM 2 must be dissolved immediately before injection, using the amount of solvent provided and stated on the label (10, 20 or 50 ml). Reconstituted KRYOBULIN TIM 2 should be used as soon as possible and in any case within 3 hours of reconstitution!

Directions for use

1. Warm the KRYOBULIN TIM 2 and solvent bottles to at least 20°C but preferably to 30°C.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.
3. Choose one of the two following procedures:

A) a) Fit a disposable needle onto a syringe of suitable size.
b) Insert the needle of the syringe into the R/C bottle with solvent and draw up the solvent into the syringe, remove the needle from the syringe.
c) Fit the enclosed filter needle onto the syringe and insert the needle somewhat eccentrically into the R/C bottle containing the lyophilisate. The vacuum in the bottle draws in the solvent.
d) Carefully dissolve the lyophilisate by gentle agitation (approx. 2—3 min.).
e) Insert the provided aeration needle and any foam will collapse. Remove the aeration needle and draw up the solution into the syringe through the filter needle provided.

B) a) Transfer of the solvent into the bottle containing the lyophilisate is done with the help of the transfer needle. For this purpose first remove the protective cap of the transfer needle and insert it into the rubber stopper of the bottle containing the solvent (fig. 2). Then remove the protective tube of the transfer needle. Turn the solvent bottle with the inserted transfer needle upside-down and insert the latter into the rubber stopper of the lyophilisate bottle leaving a free needle length of 1 cm outside the bottle (fig. 3). Caution, do not touch the needle! Because of the vacuum in the lyophilisate bottle the solvent will then run in.
b) Remove the solvent bottle **with the transfer needle** from the lyophilisate bottle (fig. 4). Gently agitate the latter in order to accelerate solution.

1 International Unit is the quantity of Factor VIII activity contained in 12.745 mg of the 2nd International Standard for Blood Coagulation Factor VIII Human, and is approximately equivalent to the Factor VIII activity in 1 ml of average normal plasma.

** Suitable human donors as described in the British Pharmacopoeia 1980, Vol. II, under Albumin.

c) Insert the provided aeration needle and any foam will collapse (fig. 5). Remove the aeration needle.

d) Fit the enclosed filter needle onto the disposable syringe and draw up the solution into the syringe (fig. 6).

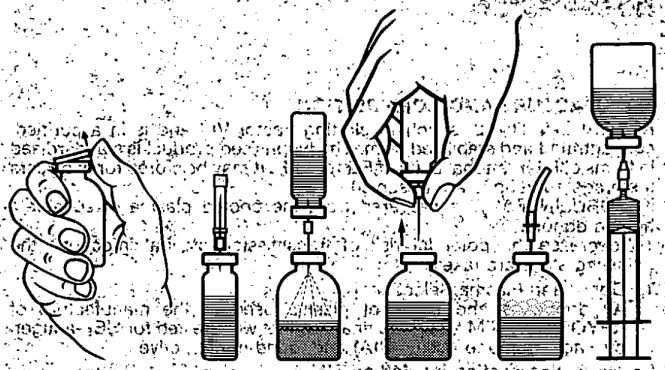

fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

4. Separate the syringe from the filter needle and fit the enclosed disposable needle (or winged adapter needle). Slowly inject the solution intravenously at a maximum rate of 5 ml/min.

Do not exceed the maximum injection rate of 5 ml/min.

The solution must be injected through a filter if a different method of reconstitution is used.

ADMINISTRATION

a) As an injection

After reconstitution of KRYOBULIN TIM 2 proceed as described in "Directions for Use, item 4.

b) As a transfusion

After reconstitution insert the filter-fitted transfusion set provided and transfuse the solution over a period of about 20 minutes.

c) Home treatment

The reconstituted KRYOBULIN TIM 2 is drawn up through the filter needle into the syringe and immediately after removal of the filter needle and insertion of the winged adapter needle with tube, the solution is administered by slow intravenous injection (maximum rate 5 ml/min.) by the patient himself or by an assistant as directed by the physician.

DOSAGE AND INDICATIONS[ref 1 6 8 9 10 11 13 14 15 17 19 24 25 28 29 30]

The amount of KRYOBULIN TIM 2 required may vary considerably according to the response of the individual. As a simple rule, to achieve an increase in the Factor VIII concentration of one percent, it is necessary to administer one i.u.* of Factor VIII per kg of bodyweight.

Initial treatment requires doses at shorter intervals than maintenance therapy, because of excessive Factor VIII consumption and replenishment of the extravascular compartment. The effectiveness of treatment should be controlled by a Factor VIII assay as partial thromboplastin time results in a less accurate value when large quantities of KRYOBULIN TIM 2 are being used. If large quantities are used, volume overloading may arise and partial removal of the patient's plasma by plasmapheresis should be considered.

Bleeding from skin, nose and oral mucous membrane

The initial dose should be 10 i.u. of Factor VIII per kg bodyweight followed by a maintenance dose of 5 to 10 i.u. of Factor VIII per kg of bodyweight at 6 to 12-hourly intervals.

Haemarthrosis

Approximately 10 i.u. of Factor VIII per kg of bodyweight should be given as an initial dose. The maintenance dose should be 5 to 10 i.u. of Factor VIII per kg of bodyweight at 6 to 12-hourly intervals. Combined with immobilisation of the affected joint for several days, the treatment should be sufficient to restore function.

Bruising

In most cases, a single dose of 10 i.u. of Factor VIII per kg of bodyweight is sufficient. With widespread bruising, repeated administration at 6 to 12-hourly intervals of 5 to 10 i.u. of Factor VIII per kg bodyweight may be required.

Heavy bleeding into muscles

Treatment should be started as soon as possible, since such bleeding may lead to permanent deformity and loss of function. Initial immobilisation of the affected area is important. The initial dose ranges from 15 to 20 i.u. of Factor VIII per kg of bodyweight followed by 10 i.u. of Factor VIII per kg of bodyweight at 6-hourly intervals from the first to the second day and at 12-hourly intervals from the third to the fifth day.

Haematuria

An initial dose of 15 to 20 i.u. of Factor VIII per kg of bodyweight will be sufficient. For maintenance, 10 i.u. of Factor VIII per kg of bodyweight should be given at 12-hourly intervals.

* 1 International Unit is the quantity of Factor VIII activity contained in 12.745 mg of the 2nd. International Standard for Blood Coagulation Factor VIII: Human, and is approximately equivalent to the Factor VIII activity in 1 ml of average normal plasma.

Major surgery on haemophilic patients

For initial treatment, the administration of at least 25 to 50 i.u. of Factor VIII per kg of bodyweight is recommended. The maintenance dose should be 20 to 40 i.u. per kg of bodyweight starting at 4-hourly intervals from the first to the fourth day and at 8-hourly intervals from the fifth to the eighth day and later, at 12-hourly intervals until all wounds are healed.

The effect of treatment must be checked daily. Factor VIII activity should not fall below 50% of the normal average value of 100%. It is important that treatment should be continued for a sufficient length of time, since the risk of a haemorrhage persists until all wounds are completely healed. Besides the repeated control of Factor VIII, tests for occasionally developing Factor VIII inhibitors should also be carried out on the patient's plasma.

Dental extractions

The amount of Factor VIII to be given depends on the number and type of teeth to be extracted and on the severity of the haemophilia.

Extraction of one or two teeth

If one or two teeth are to be extracted from a patient suffering from severe haemophilia, 10 to 20 i.u. of Factor VIII per kg of bodyweight should be administered initially. Treatment is continued at 6-hourly intervals from the first to the third day, and at 8-hourly intervals from the fourth to the eighth day after the extractions.

Extraction of more than two teeth from patients suffering from severe haemophilia

In such cases, a minimum dose of 20 to 30 i.u. of Factor VIII per kg of bodyweight should be given. Maintenance therapy should consist of doses of 10 to 20 i.u. of Factor VIII per kg of bodyweight given at 6-hourly intervals from the first to the third day, and at 8-hourly intervals for twelve more days. It is important that the plasma concentration of Factor VIII should not drop below 10%.

Prophylaxis

Prophylactic treatment should be considered for patients who bleed frequently. Dosage of approximately 20 i.u. of Factor VIII per kg bodyweight administered on alternate days may be required.

DIRECTIONS TO BE OBSERVED FOR REPLACEMENT THERAPY

As a rule replacement therapy with Factor VIII preparations is not indicated in cases of macrohaematuria and is also generally ineffective. Preference should be given to the administration of Prednisone.

If in the case of haemarthrosis, puncture of the joint is necessary, it should be carried out immediately before the first administration of KRYOBULIN TIM 2. Otherwise it might not be possible to achieve the required discharge of the articular cavity due to clot formation.

Dental extractions, injuries of the oral cavity and severe continuous nose bleeding should not be treated with KRYOBULIN TIM 2 alone but also arrested locally as far as possible. In addition, administration of anti-fibrinolytic preparations (e.g. epsilon-aminocaproic acid) is recommended in the localisation of such haemorrhages.

To avoid a decrease of the haematocrit value, administration of blood group compatible KRYOBULIN TIM 2 is recommended in cases where large doses of Factor VIII are necessary.

If haemostasis has not been reached despite administration of KRYOBULIN TIM 2 and the achievement of a sufficiently high level of Factor VIII in the patient, it is recommended that the thrombocytes function of the patient be controlled by administering blood group compatible KRYOBULIN TIM 2 along with concentrated thrombocytes.

PRECAUTIONS

Though the danger of volume overloading is small with the use of KRYOBULIN TIM 2, in cases of major surgery, control of the patient's central venous pressure, blood pressure and chest X-rays should be carried out repeatedly as required. If symptoms of volume overloading become apparent, therapeutic plasmapheresis is recommended. In patients suffering from disseminated intravascular coagulation with a significantly low Factor VIII level, this must be interrupted by the administration of HEPARIN before treatment with KRYOBULIN TIM 2 is started.

SIDE EFFECTS

Side effects are rarely observed during treatment with KRYOBULIN TIM 2 though the following reactions may occur:

1. All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with KRYOBULIN TIM 2 must be interrupted at once. Allergic reactions should be controlled with antihistamines and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls a transfusion of 5% Dextrose should be started.
2. During every type of therapy involving blood or Factor VIII concentrates, the appearance of a circulating Factor VIII antibody is possible. The time at which such an antibody is produced cannot be predicted and neither depends on the amount of Factor VIII administered nor on the frequency of administration. According to present experience, the application of corticosteroids or immunosuppressive substances has hardly influenced the formation of antibodies.
3. Despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out.

SHELF LIFE AND STORAGE

2 years when stored between 2° and 6°C or 6 months when stored at room temperature (up to +30°C).

Even without cooling facilities, KRYOBULIN TIM 2 can therefore be taken on extended journeys.