Kryobulin®

P.O.M.

Dried Human Antihaemophilic Fraction B.P.

MANUFACTURE AND COMPOSITION

KRYOBULIN is prepared from the pooled plasma of **suitable* human donors who have a GPT activity of** less than 15 i.u./l. Each plasma donation is tested by radioimmunoassay (RIA) for the absence of HB_s-antigen and is only released for the production of KRYOBULIN if the HB_s-antigen test is negative.

KRYOBULIN 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.

INDICATIONS

Prophylaxis and treatment in all cases of inherited ~~and~~/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. Under controlled treatment with KRYOBULIN, 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 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 is recommended (i.e. KRYOBULIN obtained exclusively from donors of the same blood group).

Vers. Ref.

Directions for Reconstitution of a Solution for Injection

The lyophilised KRYOBULIN must be dissolved immediately before injection using the amount of solvent provided and stated on the label (10, 20 or 50 ml).

*** Suitable human donors as described in the British Pharmacopoeia Addendum 1978 under Dried Antihaemophilic Fraction.**

** 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.**

Directions for use

1. Warm the KRYOBULIN and solvent bottles to approx. 37° C.
2. Remove the protective caps (fig. 1) and disinfect the rubber stoppers of both bottles.

3. Choose one of the two following procedures

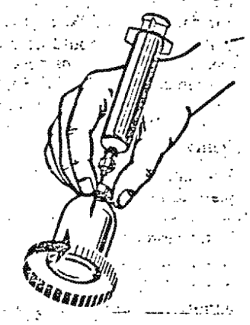
A)

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.

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).

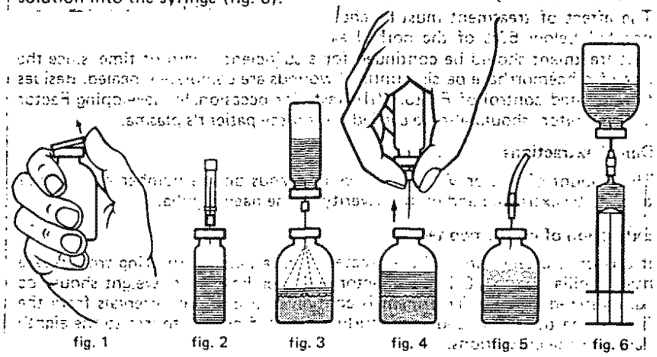


fig. 1 fig. 2 fig. 3 fig. 4 fig. 5 fig. 6

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 proceed as described in Directions for Use, item 6.

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 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 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 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.

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.

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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 a 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. 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 alone but also arrested locally as far as possible. In addition, administration of antifibrinolytic 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 is recommended in cases where large doses of Factor VIII are necessary.

If haemostasis has not been reached despite administration of KRYOBULIN 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 along with concentrated thrombocytes.

PRECAUTIONS

Though the danger of volume overloading is small with the use of KRYOBULIN, 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 is started.

SIDE EFFECTS

Side effects are rarely observed during treatment with KRYOBULIN 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 must be interrupted at once. Allergic reactions should be controlled with antihistamines and glucocorticoids 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. Despite the precautions taken in the selection and checking of donors and the testing of donations, the risk of transmission of hepatitis cannot be entirely excluded when administering human coagulation factors.
3. 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.

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 can therefore be taken along on extended journeys.

PACKS

1 R/C bottle containing lyophilised KRYOBULIN. 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.

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