TELEFAX NO: 861791 Number of pages incl. cover sheet: 11

DATE: 2.12.86

TO: Mr. Nicholson

FROM: I. Heminger

If you do not receive all of the pages
or if there are any queries, please call:

Attached please find our US pack insert of Human Albumin 5% and the revised draft pack insert of Ungebulin, Papaine treated as discussed by telephone.

Kind regards

GRO-C

# KRYOBULIN®

Dried Factor VIII Fraction B.P.
Vapour Heated (Method 3)

## COMPOSITION AND PROPERTIES

KRYOBULIN contains coagulation factor VIII (antihaemophilic globulin A) in a purified, concentrated and stabilised form. The Factor VIII content per mg protein is 1.25 to 2.5 i.u.*). The product contains 17.5 mg glucose and 10 mg glycine per ml of reconstituted solution as well as small amounts of the isoagglutinins anti-A and anti-B (max. saline titer 1 : 64). It contains not more than 64 mg fibrinogen per 100 i.u. Factor VIII.

KRYOBULIN is prepared from pooled plasma.

To decrease the potential risk of transmission of viral infections the following steps are taken:

All plasma units are exclusively obtained from Austria and Germany and the United States of America. The criteria for admission of each donor and the performance of each plasmapheresis are at least as rigorous as the respective national laws and regulations in the country of origin.

For the manufacture of KRYOBULIN only plasma units are used which are non-reactive in tests for HBs-antigen and HTLV-III antibodies.

The manufacture of KRYOBULIN includes in-process virus inactivation where vapour is applied for 10 hours at 60°C and an excess pressure of 190 mbar.

In a preclinical study to determine the virus inactivating efficacy of vapour heat treatment, samples of KRYOBULIN, which were spiked with 2 x $10^6$ infectious units of HTLV-III/ml, did not contain any detectable virus after vapour heat treatment.

## USES

KRYOBULIN is indicated for treatment and prophylaxis of all coagulation defects caused by congenital or acquired Factor VIII deficiency. These are:

— Haemophilia A
— Acquired or congenital Factor VIII deficiency with Factor VIII inhibitor
— von Willebrand's disease with Factor VIII deficiency

## CONTRAINDICATIONS

None known

## PRECAUTIONS AND WARNINGS

In disseminated intravascular coagulation associated with low Factor VIII levels Heparin should be given to interrrupt intravascular coagulation before therapy with KRYOBULIN is started.

A low incidence of adverse reactions is experienced with KRYOBULIN, but the following may occur:

All forms of allergic reaction from mild and transient urticaria to severe anaphylactic shock are possible when human plasma derivatives are administered. If such reactions occur, treatment with KRYOBULIN must be interrupted at once. Allergic reactions should be controlled with antihistamines and routine treatment given for anaphylactic shock. Monitoring of pulse rate and blood pressure is essential. If the pulse rate increases and/or blood pressure falls, transfusion of 5% Dextrose should be started.

The appearance of a circulating Factor VIII inhibitors is possible. Its appearance cannot be predicted as it does not relate to the amount of KRYOBULIN administered, nor to the frequency of administration. As far as ~~as~~ is known neither corticosteroids nor immunosuppressive agents significantly influence the formation of inhibitors.

In patients with a history of hypersensitivity reactions to plasma derivatives the prophylactic administration of antihistamines may be indicated.

If massive doses of non blood group compatible KRYOBULIN are administered over a short period of time, haemolytic reactions may occur. In severe cases of haemolysis and anaemia red blood cell concentrates should be administered.

After administration of unusually high doses as may be required in patients with Factor VIII inhibitors, the risk of hypervolaemia must be taken into consideration.

By careful selection of donors and plasma and the vapour heat treatment process, the transmission of HTLV-III can be excluded.

The above measures will certainly reduce the risk of transmission of viral hepatitis but this cannot be entirely ruled out.

### INTERACTIONS

None known

### DOSAGE AND ADMINISTRATION

**Dosage**

**I. Haemophilia A**

**1. Spontaneous Bleeding**

Individual dosage depends on the severity of the Factor VIII defect, the localisation and the extent of the haemorrhage. The severity of haemophilia is judged by the residual Factor VIII plasma concentration of the patient. Table 1 shows the Factor VIII levels (in % of normal) required for the management of individual types of bleeding.

* 1 I.U. Factor VIII (according to WHO standard) corresponds to the activity of factor VIII in 1 ml of fresh average human plasma.

→ auf S 1

| Type of bleeding | Factor VIII plasma level to be achieved by initial dose | Factor VIII level during maintenance therapy | Duration of maintenance of indicated Factor VIII level |
|---|---|---|---|
| **Minor haemorrhage:** e.g. Early stage of joint and muscle bleeding, epistaxis, bleeding into the oral cavity and minor trauma, haematuria | 30% | 30% | 1—3 days |
| **Major haemorrhage:** e.g. Haemarthrosis or haematoma with pain and swelling, head trauma without neurological signs, severe trauma also without open bleeding, gastrointestinal bleeding, heavy abdominal pain, major surgery | 50% | 30—50% | 3—4 days or until adequate wound healing |
| **Life-threatening haemorrhage:** e.g. Intracranial, intraabdominal or intrathoracic bleeding, severe injury, fractures | 80% | 30—50% | 10—14 days or until adequate wound healing |

**Table 1:** Therapeutically required Factor VIII plasma level (in % of normal) for haemophilia A patients.

To achieve the Factor VIII plasma levels indicated in table 1, dosage may be calculated according to the formula:

1 I.U./kg bodyweight → Factor VIII plasma level increase of 1% (loading dose to obtain initial Factor VIII levels indicated)
2% (repeat dose to obtain Factor VIII levels indicated for maintenance therapy)

The residual Factor VIII activity of the patient must be taken into consideration when calculating the dose.

| Bodyweight kg | Plasma level increase, % | | | | |
|---|---|---|---|---|---|
| | 20% | 30% | 40% | 50% | 60% |
| 10 | 200 | 300 | 400 | 500 | 600 |
| 15 | 300 | 450 | 600 | 750 | 900 |
| 20 | 400 | 600 | 800 | 1000 | 1200 |
| 25 | 500 | 750 | 1000 | 1250 | 1500 |
| 30 | 600 | 900 | 1200 | 1500 | 1800 |
| 35 | 700 | 1050 | 1400 | 1750 | 2100 |
| 40 | 800 | 1200 | 1600 | 2000 | 2400 |
| 45 | 900 | 1350 | 1800 | 2250 | 2700 |
| 50 | 1000 | 1500 | 2000 | 2500 | 3000 |
| 55 | 1100 | 1650 | 2200 | 2750 | 3300 |
| 60 | 1200 | 1800 | 2400 | 3000 | 3600 |
| 65 | 1300 | 1950 | 2600 | 3250 | 3900 |
| 70 | 1400 | 2100 | 2800 | 3500 | 4200 |
| 75 | 1500 | 2250 | 3000 | 3750 | 4500 |
| 80 | 1600 | 2400 | 3200 | 4000 | 4800 |

**Table 2:** Loading doses for initial application in I.U. Factor VIII based on a 1% increase in the Factor VIII level after injection of 1 I.U. Factor VIII/kg bodyweight.

The half life of Factor VIII is 8 — 12 hours, and the in vivo recovery ranges between 60 — 80%. The minimum haemostatic level to prevent bleeding is 30% of normal. Thus, KRYOBULIN should be given at intervals of 8 — 24 hours depending on the individual bleeding situation.

In general, minor bleeding can be controlled by a single application. Otherwise, a second application of one third of the loading dose should be made after 24 hours. Major haemorrhage should be treated at 8 — 12 hour intervals with one half of the loading dose to prevent a decrease of the Factor VIII plasma level below 30% towards the end of the substitution intervals. Substitution therapy with KRYOBULIN must be continued until complete resorption of tissue haemorrhage or adequate wound healing.

**2. Surgery**

For elective surgery dosage calculations should allow for the fact that normally there is no increased consumption of Factor VIII prior to surgical interventions, whereas during an operation and in the early postoperative hours the Factor VIII consumption is considerably increased. Substitution treatment should be commenced 1 — 2 hours prior to the surgical intervention.

| Surgery | Preoperative Factor VIII level | Postoperative Factor VIII level | |
|---|---|---|---|
| Minor surgery (e.g. dental extractions) | 50% | 50% | Day of operation |
| | | 30 — 50% | until adequate wound healing |
| Major surgery | 80% | 80% | Day of operation |
| | | 50% | First week postoperatively |
| | | 30% | From the second week postoperatively until adequate wound healing |

**Table 3:** Therapeutically required Factor VIII level (in % of normal) for surgical interventions.

To achieve the Factor VIII levels indicated in table 3, dosage may be calculated according to the formula:

1 I.U./kg bodyweight — Factor VIII plasma level increase of
2% (prior to surgery)
1 — 2% (after surgery)

The residual Factor VIII activity of the patient must be taken into consideration when calculating the dose.

Postoperatively substitution intervals of 8 — 12 hours should be adhered to. For monitoring the clinical course and calculation of the precise dose required close laboratory control of the patient's Factor VIII plasma level must be performed. Individual dosage must be calculated so as to exclude any decrease of the Factor VIII level below 30% towards the end of the substitution interval in order to prevent bleeding complications, delayed wound healing and serious sequelae.

**3. Long Term Prophylactic Treatment**

For long term prophylactic substitution of Factor VIII, either 12 I.U. Factor VIII/kg bodyweight at intervals of 2 — 3 days or 30 I.U. F VIII/kg bodyweight at intervals of 3 — 4 days are recommended.

**II. Acquired or Congenital Factor VIII Deficiency with Factor VIII Inhibitor**

In patients with circulating inhibitors against Factor VIII any substitution treatment with Factor VIII concentrate should only be carried out to control severe bleeding. To obtain the required plasma concentration of Factor VIII unusually high doses of KRYOBULIN may have to be administered, since part of the infused Factor VIII is inactivated by the inhibitor (Warning: volume overload!). As a general rule Factor VIII substitution in patients with an inhibitor is therefore **not** recommended with Factor VIII inhibitor titres of more than 5 Bethesda Units/ml.

Independent of the inhibitor titre the use of FEIBA® IMMUNO * has proved effective in patients with Factor VIII inhibitors.

Close laboratory control of the Factor VIII plasma level to monitor the clinical course and to calculate the individual dose required is indispensable in the treatment of acquired or congenital Factor VIII deficiency with Factor VIII inhibitor.

**III. Von Willebrand's Disease with Factor VIII Deficiency**

KRYOBULIN may be used for treatment of bleeding complications and surgical interventions in von Willebrand patients if cryoprecipitate is not available or if a history of allergic reactions following the use of cryoprecipitate necessitates a change of product. In case of surgery substitution treatment with KRYOBULIN should be started already 12 hours prior to the surgical intervention.

Dosage and substitution intervals depend on the laboratory controls.

**Additional Instructions**

With dental extractions, trauma in the oral cavity and severe, prolonged epistaxis, local haemostatic control should be attempted in addition to replacement therapy with KRYOBULIN.

Antifibrinolytics (e.g. epsilonaminocaproic acid) are are also indicated in local bleeding.

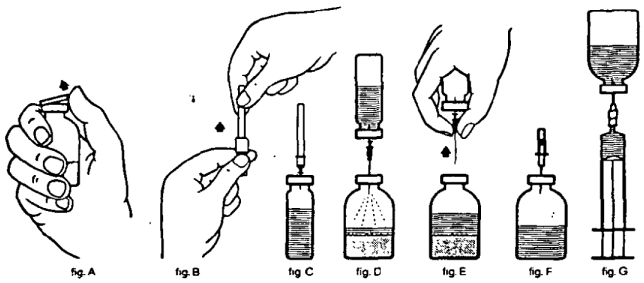
In exceptional cases of severe haemarthroses aspiration may be necessary. Treatment with KRYOBULIN should then be started immediately following aspiration. KRYOBULIN must not be given before aspiration or a clot may form in the synovial cavity.

**Reconstitution of Concentrate**

KRYOBULIN should be stored in the lyophilised form and should only be reconstituted immediately before application. The solution must then be used promptly. Entered vials must not be reused.

* FEIBA® IMMUNO Factor Eight Inhibitor Bypassing Fraction Human, Vapour Heated

1. Warm the unopened bottle containing the solvent to room temperature (max. 37°C).
2. Remove the caps from the concentrate and solvent bottles (fig. A) and disinfect the rubber stoppers of both bottles.
3. The enclosed transfer needle (double-ended needle) is protected by 2 plastic caps sealed by a weld mark. Break the weld (fig. B) by twisting and remove one cap. Insert the exposed needle into the rubber stopper of the solvent bottle (fig. C).
4. Remove the other cap from the double-ended needle taking care not to touch the exposed end.
5. Invert the solvent bottle over the concentrate bottle, and insert the free end of the double-ended needle to approximately half the needle length into the rubber stopper of the concentrate bottle (fig. D). The solvent will be drawn into the concentrate bottle which is under vacuum.
6. Disconnect the two bottles by removing the needle from the concentrate bottle (fig. E). Agitate or rotate the concentrate bottle to accelerate reconstitution.
7. Upon complete reconstitution of the concentrate insert the enclosed aeration needle (fig. F) and any foam will collapse. Remove the aeration needle.




**Administration**

Remove the protective covering from the enclosed filter needle by turning the cap and fit the needle onto a sterile disposable syringe. Draw the solution into the syringe (fig. G).

Disconnect the filter needle from the syringe and slowly (maximum rate of injection: 5 ml/min.) inject the solution intravenously with the enclosed disposable needle (or the infusion set with a winged adapter).

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

For home treatment make sure that following injection of KRYOBULIN the protective covering is put on all needles (uncovered needles may injure other persons) and the needles together with the syringes are disposed of according to the guidance of haemophilia centre staff.

## SHELF LIFE AND STORAGE

Two years when stored between + 2° and + 8°C.

Within the indicated shelf life period the product may be stored for 6 months at room temperature (max. 30°C). Even without cooling facilities KRYOBULIN can therefore be taken on extended journeys.

The dates between which the product is not stored at refrigerator temperature should be noted on the package.

KRYOBULIN TIM 3 must not be used beyond the expiry date indicated.

Store out of the reach of children.

**PACKS**

KRYOBULIN TIM 3

— R/C vial containing 250 I.U. of lyophilised F VIII
— R/C vial containing 10 ml Water for Injections B.P.

— R/C vial containing 500 I.U. of lyophilised F VIII
— R/C vial containing 20 ml Water for Injections B.P.

— R/C vial containing 1000 I.U. of lyophilised F VIII
— R/C vial containing 40 ml Water for Injections B.P.

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