Treatment of overdosage
No specific side effects have been reported following overdosage with Kryobulin (Factor VIII-activity above 120%). The half life of about 12 hours will rapidly normalise Factor VIII-activity in the patient.

pharmaceutical precautions: Kryobulin must be stored between +2°C and +6°C, and protected from the light. It then has a shelf-life of two years. When stored between +20°C and +30°C it has a life of six months.

legal category: P.O.M.

package quantity: **KRYOBULIN HOME TREATMENT PACK**
Each pack contains:
1 rubber capped vial containing 250 or 500 i.u. Dried Factor VIII Fraction B.P.
1 rubber capped vial containing Water for Injections BP.
This pack also contains a syringe, I/V needles, winged adaptor needle, filter needle, venting needle and swabs.

KRYOBULIN HOSPITAL PACK
Each pack contains:
1 rubber capped vial containing 1,000 i.u. Dried Factor VIII Fraction B.P.
1 rubber capped vial containing Water for Injections BP.
The pack also contains a filter needle and venting needle.

further information: Kryobulin is especially suitable for Home Treatment. Packs contain all requirements and can be stored in a domestic refrigerator for two years and for up to six months at room temperatures not exceeding 30°C.

Effect on laboratory tests
Laboratory tests influenced in patients treated with Kryobulin are: Factor VIII assays; activated PTT; Fibrinogen determination according to Clauss.

product licence number, name and address:
Product Licence Number:
0215/0003

Product Licence Holder:
Immuno Limited,
Arctic House, Rye Lane, Dunton Green,
Nr Sevenoaks, Kent TN14 5HB
Tel. No: Sevenoaks (0732) 458101
Telex No: 95413

date of preparation: March 1985

Kryobulin is a registered trade mark.

Heat Treated
Dried Factor VIII Fraction B.P.

Immuno Ltd

DATA SHEET

name of product: KRYOBULIN™ HEAT TREATED
Dried Factor VIII Fraction B.P.

presentation: Dried Factor VIII Fraction B.P. is a white to yellowish amorphous powder or friable solid without any characteristic odour.

It is prepared from the plasma of suitable human donors† whose donations are shown by R.I.A. to be free from HB_sAg. Pooled plasma and the final product are also tested for freedom from HB_sAg.

The product has been heated at 60°C for 10 hours. This step has been introduced to reduce the risk of transmission of infectious agents.

It is packed in vials each containing approximately 250, 500 or 1000 International Units of Factor VIII. Separate vials of Water for Injections B.P. are provided for reconstitution.

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

uses: Kryobulin corrects Factor VIII deficiency, and is used in the treatment of bleeding due to such deficiency in:
Haemophilia A
von Willebrand's disease
Haemophilia complicated by Factor VIII inhibitors

dosage and administration: Frequent tests of the patient's plasma level of Factor VIII must be made to allow correction of the deficiency by administration of Kryobulin but for guidance an estimation of the required dosage can be made by the following calculation:

To achieve an increase of Factor VIII concentration of 1% it is necessary to administer 1 i.u. of Kryobulin per kg bodyweight, both for adults and children.

Initial treatment requires doses to be given at shorter intervals than in maintenance therapy, to provide an initial high level of activity and to replenish the extravascular compartment.

† Human donors as described in the British Pharmacopoeia 1980 Vol II under Albumin

Bleeding from skin, nose and oral mucous membrane:
Initial dose should be 10 i.u./kg at intervals of 6 to 12 hours.

Haemarthrosis:
The initial dose should be approximately 10 i.u./kg and the maintenance dose 5 to 10 i.u. per kg at intervals of 6 to 12 hours. 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./kg is sufficient. For widespread bruising, repeated administration of 5 to 10 i.u./kg at intervals of 6 to 12 hours may be required.

Heavy bleeding into muscles:
Immediate treatment is required to prevent permanent deformity and loss of function, and initial immobilisation of the affected area is important. An initial dose of 15 to 20 i.u./kg should be given, the maintenance dose to be 10 i.u./kg at intervals of 6 hours from the first to the second day, and at intervals of 12 hours from the third to the fifth day.

Haematuria:
The initial dose should be 15 to 20 i.u./kg, and the maintenance dose 10 i.u./kg at intervals of 12 hours.

Major surgery on haemophilic patients:
The initial dose should be at least 25 to 50 i.u./kg, and the maintenance dose 20 to 40 i.u./kg at intervals of 4 hours from the first to the fourth day, of 8 hours from the fifth to the eighth day, and of 12 hours until all wounds are healed.

The effect of treatment must be checked daily. Factor VIII activity should not be allowed to fall below 50% of the normal 100% average value. It is important that treatment be continued until all wounds have healed completely, as the risk of haemorrhage persists till then.

In addition to monitoring Factor VIII activity, tests for the development of Factor VIII inhibitors should also be made.

Dental extractions:
The required dosage depends on the number and type of teeth to be extracted, and on the severity of the haemophilia. If **one or two teeth** are to be extracted from a patient with severe haemophilia, an initial dose of 10 to 20 i.u./kg should be given. Maintenance treatment with this dosage at intervals of 6 hours from the first to the third day, and 8 hours from the fourth to the eighth day after extraction, should be given. If **more than two teeth are to be extracted from patients with severe haemophilia**, a minimum initial dose of 20 to 30 i.u./kg should be given, and a maintenance dose of 10-20 i.u./kg at intervals of 6 hours from the first to the third day, and of 8 hours for twelve more days. The plasma concentration of Factor VIII should not be allowed to fall below 10% of the normal 100% average value.

Factor VIII assays should be used to monitor the effectiveness of treatment, as partial thromboplastin time gives a less accurate value when large quantities of Kryobulin are being used.

Solutions of Kryobulin must be administered intravenously, at a rate not exceeding 10 ml in 3 minutes.

Use in the elderly

No specific precautions or side effects have to be taken into account in the elderly.

Use in pregnancy

The use of Kryobulin need not be restricted during pregnancy.

contra-indications warnings, etc.:

Although the danger of volume overload is small with Kryobulin, during major surgery monitoring of the patient's central venous pressure and blood pressure, and serial chest X-rays, may be advisable.

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

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

1 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.

2 Despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out.

3 The appearance of a circulating Factor VIII inhibitor 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 is known neither corticosteroids nor immunosuppressive agents significantly influence the formation of inhibitors.