

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 2×10^6 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

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

PRECAUTIONS AND WARNINGS

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 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.

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 type O whole blood or red blood 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

1. 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.

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:

$$1 \text{ I.U./kg bodyweight} - \text{Factor VIII plasma level increase of } 2\% \text{ (prior to surgery)} \\ 1 - 2\% \text{ (after surgery)}$$

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^R 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 also indicated in local bleeding.

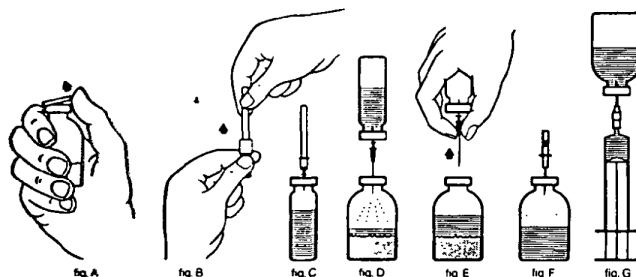
In exceptional cases of severe haemarthroses aspiration may be necessary. Treatment with KRYOBULIN should then be started immediately following aspiration. KRYOBULIN must not be given before aspiration or a clot may form in the synovial cavity.

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^R 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 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.

REFERENCES

1. Richard D. Aach, M.D., Wolf Szmunes, M.D., James W. Mosley, M.D., F. Blaine Hollinger, M.D., Richard A. Kahn, Ph.D., Cladd E. Stevens, M.D., Virginia M. Edwards, B.S., Jochewed Werch, M.D.: Serum Alanine Aminotransferase of Donors in Relation to the Risk of Non-A, Non B Hepatitis in Recipients. The Transfusion-Transmitted Viruses Study. The New England Journal of Medicine, Vol. 304 (no. 17): 989 - 994, 1981
2. Louis M. Aledort, M.D., Steven Taub, Michael Diaz, M.D.: Problems of Anti-A and Anti-B in Concentrates. In: M. Hilgartner (ed): Hemophilia in the Child and Adult. Mason, New York, 1982: 181 - 185
3. Harvey J. Alter, M.D.: Robert H. Purcell, M.D., Paul V. Holland, M.D., David W. Alling, M.D., Deloris E. Koziol, M.T.(ASCP): Donor Transaminase and Recipient Hepatitis. Impact on Blood Transfusion Services. Jama, Vol. 246 (no. 6): 630 - 634, 1981
4. A. Aronstam, D.S. McLellan, M. Wassef, P.S. Mbatha: Effect of height and weight on the in vivo recovery of transfused factor VIII C. J. Clin. Pathol., 35: 289 - 291, 1982
5. Arthur L. Bloom: Current Status and Trends in the Treatment of Hemophilic Patients with Inhibitors. In: Menache, Surgenor, Anderson (eds): Hemophilia and Hemostasis. Alan R. Liss, Inc., New York, 1981: 123 - 138
6. A.L. Bloom, I.R. Peake, R.A. Furlong, B.L. Davies: High Potency Factor VIII Concentrate: More Effective than Cryoprecipitate in a Patient with Von Willebrand's Disease and Inhibitor. Thrombosis Research 16: 847 - 852, 1979
7. Eibl H., Dorner F., Barrett N.: Inactivation of HTLV-III/LAV in coagulation factor concentrates by steam treatment. Abstracts from the XVII International Congress of the World Federation of Hemophilia, Milano, 1986. P.M. Mannucci, A. Gringeri, M. Moia (eds): Research in Clinic and Laboratory, Vol. XVI (no. 1), 1986: Abstract no. 91

8. Sydney S. Gellis, John R. Neefe, Joseph Stokes, J.R. Lawrence, E. Strong, Charles A. Janeway, George Scatchard: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. XXXVI. Inactivation of the Virus of Homologous Serum Hepatitis in Solutions of Normal Human Serum Albumin by Means of Heat. Journ. of Clin. Invest., Vol. 27: 239 - 244, 1947
9. Edward D. Gomperts: Procedures for the Inactivation of Viruses in Clotting Factor Concentrates. American Journal of Hematology 23: 295 - 305, 1986
10. Carol K. Kasper: Factor VIII Concentrates: Kinetics In Vivo, Dosage and Demand. In: Mammen, Barnhart, Lusher and Walsh (eds): Treatment of Bleeding Disorders. PJD Publications Ltd, Westbury, N.Y., 1980: 57 - 66
11. Carol K. Kasper, M.D.: In Vivo Recovery of F VIII: C in Hemophilic Patients. In I.M. Nilsson, T.W. Barrowcliffe, Kl. Schimpf (eds): Factor VIII Concentrates and their Clotting Activity. Scandinavian Journal of Haematology, Suppl. 41, Vol. 33: 147 - 154, 1984
12. H. Kjellman: Calculations of Factor VIII in vivo Recovery and Half-life. Scand J Haematol, Suppl. 40, Vol. 33: 165 -174, 1984
13. M. Köhler, P. Hellstern, E. Wenzel: The Use of Heat-Treated Factor VIII-Concentrates in von Willebrand's Disease. Blut 50: 25 - 27, 1985
14. Giovanni Longo, Marzia Matucci, Andrea Messori, Massimo Morfini, Pierluigi Rossi-Ferrini: Pharmacokinetics of a New Heat-Treated Concentrate of Factor VIII Estimated by Model-Independent Methods. Thrombosis Research, 42: 471 - 476, 1986
15. M. Morfini, A. Messori, G. Longo, S. Cinotti, M. Matucci, P. Rossi Ferrini: Half-Life and In-Vivo Recovery of Heated Factor VIII Concentrates. The Lancet, Sept. 6: 571 - 572, 1986
16. G. Norkraus, A. Widell, A.-C. Teger-Nilsson, H. Kjellman, G. Frösner, S. Iwarson: Acute Hepatitis Non-A, Non-B following Administration of Factor VIII Concentrates. Vox Sang, 41: 129 - 133, 1981

17. Jan Over, Jan J. Sixma, Marijke H.M. Doucet-de Bruine, Annemieke M.C. Trieschnigg, Riek A.A. Vlooswijk, Nel H. Beeser-Visser, Bonno N. Bouma: Survival of ¹²⁵Iodine-Labeled Factor VIII in Normals and Patients with Classic Hemophilia. Observations on the Heterogeneity of Human Factor VIII. J. Clin. Invest., Vol. 62: 223 - 234, 1978
18. C.R. Rizza: Management of patients with inherited blood coagulation defects. In: Arthur L. Bloom, Duncan P. Thomas (eds): Haemostasis and Thrombosis. Churchill Livingstone, Edinburgh, 1981: 371 - 388
19. Kl. Schimpf, P. Rothmann, K. Schumacher: Comparison of Factor VIII Concentrates in Non-Bleeding Patients. In: I.M. Nilsson, T.W. Barrowcliffe, Kl. Schimpf (eds): Factor VIII Concentrates and their Clotting Activity. Scandinavian Journal of Haematology, Suppl. 41, Vol. 33: 131 - 145, 1984
20. V. Tilsner, H. Reuter: Side effects of Factor VIII substitution in patients with haemophilia A. Münchner Medizinische Wochenschrift, 124 (22): 553 - 557, 1982
21. Theodore S. Zimmerman, Zaverio M. Ruggeri: Von Willebrand's Disease. Clinics in Haematology, Vol. 12 (no. 1): 175 - 200, 1983

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