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INFECTED BLOOD INQUIRY

EXHIBIT WITN1425002

DRIED FACTOR VIII FRACTION (Intermediate Specific Activity Concentrate)

This fraction is a concentrate of human blood coagulation factor VIII prepared from the plasma of voluntary blood donors by methods as described by Smith et al (1979), based on those of Newman et al (1971) and James and Wickerhauser (1972). It is prepared on behalf of the Department of Health and Social Security in laboratories at Elstree and Oxford (headquarters, Blood Products Laboratory, Elstree, Herts. WD6 3BX). The name of the manufacturing laboratory is stated on label.

The fraction is normally available only through Haemophilia Centres which have the assay facilities needed to monitor its use. The treatment of patients with deficiencies of coagulation factors requires clinical expertise and, whether undertaken at hospital or at home, should always be directed by a doctor experienced in the management of haemorrhagic disorders.

Storage:

The label carries the instruction: "Store in the dark at below -46°C". Short periods of storage at normal ambient temperature are not deleterious.

Potency:

The label carries a statement of the activity in terms of blood coagulation factor VIII expressed in International Units (IU), as established by the World Health Organization.

Reconstitution:

The container of concentrate and the water for solution should be brought to 20°-30° C. The volume of Water for Injections indicated on the product label is then added to the freeze-dried material, and the container is agitated gently until solution is complete. A clear or slightly opalescent solution is usually obtained in about fifteen minutes or less. If a gel or clot forms discard the solution and inform the laboratory whose address is on the product. Should more than one bottle be required to make up the dose, the contents of the required number are pooled. As the factor is unstable, the solution should be used immediately.

Dose:

The number of units needed and duration of treatment depend on the lesion being treated. If the rise in the concentration of factor VIII in the plasma following administration of concentrate is expressed in international units per 100 ml plasma and the total dose given in international units of factor VIII per kg body weight is calculated, "the response" is defined as follows:-

$$\text{Response} = \frac{\text{Rise in plasma factor VIII (in IU per 100 ml)}}{\text{Dose in IU/kg body weight}}$$

The 'theoretical value' for this ratio (2.4) is rarely reached. It is variable even in the same patient, a range of 1.6 - 2.2 is usual but values outside this range may be found. A low value may indicate that the patient's plasma contains an antibody to factor VIII and appropriate tests should be done.

The following table indicates the approximate levels of factor VIII required for haemostasis in various circumstances.

Lesion	Concentration of factor VIII desired in patient's blood immediately after transfusion (per 100 ml)	Initial dose of factor VIII (IU/kg body weight)
Minor spontaneous haemarthrosis, and muscle haematomas	15 to 20	7 to 13
Severe haemarthrosis and muscle haematomas, haematoma in potentially dangerous situations, haematuria	20 to 40	8 to 25
Major surgery	See below	

A dose of 1 u/kg will give, on average, a rise of about 2 u/100 ml plasma. If the desired concentration or clinical response is not achieved, another dose should be given the same day. If an abnormally low response persists, carry out a test for specific antibody to factor VIII. The doses mentioned are only rough guides since there is considerable variation in response from patient to patient. It is usual to give the contents of the number of whole bottles nearest to the calculated dose. Doses may be repeated at intervals of 8, 12 or 24 hours as needed to maintain the desired concentration of factor VIII.

Major surgery

Major surgery should be undertaken only where there are facilities for assaying factor VIII so that the patient's response can be assessed. The patient's plasma should be tested for antibody to factor VIII before operation. If antibody is not present, a pre-operative dose of 35 to 50 u per kg is given to raise the plasma factor VIII concentration to 80% or more of average normal. During the first few days after operation the plasma factor VIII concentration is monitored and the dose repeated 8-hourly or 6-hourly as needed, so that the concentration does not fall below 30-50% of average normal. After the first few days the frequency of the dose may be reduced. The course of treatment is usually continued for ten days or longer.

As indicated previously, if the plasma factor VIII concentration does not reach the expected level, or falls off with a reduced half-life (less than twelve hours), the presence of an antibody to factor VIII should be suspected and the appropriate laboratory tests done. The treatment of patients with antibodies to factor VIII is outside the scope of these notes.

Administration:

The solution should be drawn from the vial into a plastic disposable syringe through the filter needle supplied with the product. For administration, a No. 21 "butterfly" needle is convenient. Although the material rarely causes side effects, the dose, especially the first dose, should be given slowly (approximately 3 ml per minute). The solution must not be stored and infusion should be completed within three hours of reconstitution. It should not be given by "continuous infusion" over many hours, and it must not be added to any other fluid given, including whole blood.

Warnings:

(1) The material contains blood group antibodies derived from the starting plasma in amounts which are insignificant in the normal treatment of haemarthroses and muscle haemorrhage. If very high dosage is necessary in patients with blood groups A, B or AB, the patient should be monitored for signs of intravascular haemolysis.

(2) All donations of blood from which plasma is derived for the preparation of factor VIII are screened for the presence of HBsAg by radioimmunoassay or reversed passive haemagglutination and, in addition, each batch of factor VIII concentrate is tested by radioimmunoassay. Nevertheless the most sensitive tests cannot eliminate the possibility that the fraction may be infective. Therefore the risk of transmitting hepatitis cannot be disregarded.

(3) Patients congenitally deficient in factor VIII may develop antibodies to factor VIII following treatment. This risk does not appear to be increased by the use of concentrate (Biggs, 1974) but patients should be monitored from time to time, especially if there is any doubt about the clinical effectiveness of a dose of factor VIII.

References:

- Biggs, R. (1974) Jaundice and antibodies directed against factor VIII and IX in patients treated for leukaemia or Christmas disease in the United Kingdom. *British Journal of Haematology*, 28, 313-329.
- Newman, J., Johnson, A. J., Karpitkin, M. H. & Puszkin, S. (1971) Methods for the preparation of clinically effective intermediate- and high-purity factor VIII concentrates. *British Journal of Haematology*, 21, 1-20.
- James, H. L. & Wickerhauser, M. (1972) Development of large-scale fractionation methods III. Preparation of a factor VIII concentrate of intermediate-purity. *Vox Sanguinis* 23, 402-412.
- Johnson, A. J., Karpitkin, M. H. & Newman, J. (1971) Clinical investigation of intermediate- and high purity anti-haemophilic factor (factor VIII) concentrates. *British Journal of Haematology*, 21, 21-41.
- Smith, J. K., Evans, D. R., Stone, V. & Snape, T. J. (1979) A factor VII concentrate of intermediate purity and higher potency. *Transfusion*, 19, 299-306.

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Product Licence Nos. 0134/0007-8

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