INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

EXHIBIT WITN6984041

Interoffice Communication

MILES

Cutter Laboratories
STOKE COURT

Date 17th April, 1985.

To See distribution list

From Linda Frith

Subject Koate HT Data Sheet

Copy to B. Dyos
W. Marzouk

Attached is the approved Data Sheet for Koate HT.

The Data Sheet will be sent to all prescribing clinicians when UK labelled and NIBSC approved product is available for sale in the U.K. The current shipment schedule indicates this to be the end of July, 1985.

Send minimal Data Sheet to DHSS later ... when selling - July?

Linda A. Frith

GRO-C to send out copy of covering letter & enclosure

To: Marie Tatt
Brian Elliott
Gordon Tuck

Cutter

LEGAL CATEGORY

P.O.M.

PACKAGE QUANTITIES

Each pack contains:—
One single-dose vial of Factor VIII Fraction containing approximately 250, 500, 1,000 or 1,500 IU's, one vial of the appropriate quantity of Water for Injection, a sterile filter needle and a sterile double-ended transfer needle.

FURTHER INFORMATION

After infusion of Factor VIII, there is an instantaneous rise in the coagulant level, followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity. The early rapid phase may represent the time of equilibrium with the extravascular compartment, and the second or slow phase of the survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused Factor VIII. Studies with Koate–HT in haemophiliacs have demonstrated an initial 50% disappearance time of five hours, and a biologic half-life of approximately 13 hours. There were not significant differences between bleeding and non-bleeding patients.

Koate–HT has been heated at 68°C for 72-77 hours and there is no evidence of any adverse effect upon the properties of the product. The heat treatment step has been introduced to reduce the risk of transmission of infectious agents.

Studies have demonstrated that the heat-treatment process used in the production of Koate–HT inactivates potential infectious viruses, including a retrovirus, but it has not yet been established that agents of any major transmittable disease would be inactivated.

PRODUCE LICENCE No.

PL 0055/0107

NAME AND ADDRESS OF LICENCEE

Cutter Division,
Miles Laboratories Limited,
Stoke Court,
Stoke Poges,
Slough,
Berkshire,
SL2 4LY

Cutter

*Trade mark of Miles Laboratories Inc., U.S.A.

February 1985

DATA SHEET

NAME OF PRODUCT

KOATE*–HT
Dried Factor VIII Fraction Heat-treated

PRESENTATION

Koate–HT is a stable purified dried concentrate of human Factor VIII (Antihaemophilic Factor) prepared from the cold insoluble fraction of pooled fresh-frozen plasma. When reconstituted with Water for Injection, it contains 25-40 times as much Factor VIII as an equal volume of fresh plasma. Koate–HT has been heat-treated at 68°C for 72-77 hours.

Koate–HT is a white, sterile, lyophilised powder presented in vials containing approximately 250, 500, 1,000 or 1,500 International Units of Factor VIII. One International Unit (IU) is defined by the use of the World Health Organisation Standard for Blood coagulation Factor VIII, human.

A vial containing a suitable volume of Sterile Water for Injection, a sterile filter needle and a sterile double-ended transfer needle are also provided.

USES

For the treatment of classical haemophilia (haemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koate–HT provides a means of temporarily replacing missing clotting factor in order to correct or prevent bleeding episodes or in order to facilitate emergency and elective surgery on haemophiliacs. Dried Factor VIII Fraction is not effective in the treatment of Von Willebrand's disease.

DOSAGE & ADMINISTRATION

Dosage

Each vial of Koate–HT has the Factor VIII activity in IU's stated on the label.

The following formulae provide a guide for dosage calculations:-

Expected Factor VIII increase (in % of normal =

$$\frac{\text{IU administered} \times 2.0}{\text{body weight (in kg)}}$$

It should be emphasised, however, that all efforts should be made to follow the course of therapy with Factor VIII level assay. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained.

Mild to moderate haemorrhages may be treated with sufficient Koate–HT to raise the plasma Factor VIII level to 20-30% of normal. If the haemorrhage is moderate or if minor surgery is contemplated, a level of 30-50% of normal should be achieved. Severe haemorrhage may require levels of 80-100% of normal in order to achieve haemostasis. Single doses may suffice for treatment of mild haemorrhage, but more severe illness may require multiple daily doses to achieve desired levels.

It should be emphasised that the above dosage recommendations are presented for guidance. The dosage required for normalising haemostasis must be determined according to the needs of the individual patient.

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Thus, factors to be considered include the weight of the patient, the severity of the deficiency, the severity of haemorrhage, the presence of inhibitors and the Factor VIII level desired. All efforts should be made to follow the course of therapy with Factor VIII level assays.

The clinical effect of Factor VIII on the patient is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koate–HT than would be estimated in order to attain satisfactory clinical results. If the Factor VIII level fails to attain that expected, or if bleeding is not controlled after adequate calculated dosage, the presence of Factor VIII inhibitor should be suspected. Its presence should be confirmed and the inhibitor level quantitated by appropriate laboratory procedure. When an inhibitor is present, the dosage requirement for Factor VIII is extremely variable and the dosage can be determined only the the clinical response.

Reconstitution and Administration

1. Warm the unopened diluent (Sterile Water for Injection USP) and Factor VIII concentrate to room temperature but not higher than 37°C, 99°F.
2. Remove the plastic flip-top caps from both bottles and cleanse the rubber stoppers with a suitable antiseptic immediately before each piercing.
3. Remove the protective cover from one end of the double-ended transfer needle. Insert exposed needle into stopper of diluent bottle.
4. Remove the protective plastic from the other end of the needle. Invert the diluent bottle and insert exposed needle into stopper of the concentrate bottle.
5. The vacuum will transfer the diluent into the concentrate bottle. Hold the concentrate bottle at an angle to the diluent bottle in order to direct the jet of diluent against the wall of the concentrate bottle. Avoid excessive foaming. Do not shake the concentrate bottle at any time. If the vacuum is not present, the diluent will not flow and that bottle should not be used.
6. After removing the diluent bottle and needle, very gently rotate the Koate–HT bottle in order to dissolve the concentrate.
7. After the concentrate is completely dissolved, withdraw the Koate–HT solution into the syringe through the filter needle which is supplied in the package. Replace the filter needle with an appropriate sterile injection needle, e.g., 21 gauge x 1 inch, and inject intravenously.
8. If the same patient is to receive more than one bottle of Koate–HT the contents of two bottles may be drawn into the syringe through filter needles before attaching the injection needle.

CONTRA INDICATIONS, WARNINGS, ETC.

Contraindications

There are no specific contraindications to the use of Dried Factor VIII Fraction. (Please read Uses section carefully before use).

Precautions

1. Koate–HT is intended for the treatment of bleeding disorders arising from a deficiency of Factor VIII. This deficiency should be proven prior to administering Koate–HT, since no benefit may be expected from its use in treating other causes of haemorrhage.
2. After reconstitution, administer as promptly as possible and within 3 hours. Do not refrigerate after reconstitution. NOTE : Koate–HT is fully stable without potency loss for at least 24 hours at room temperature after reconstitution. The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koate–HT, in the unopened vial, is sterile.
3. Administer only by the intravenous route.
4. A filter needle should always be used for transfer to syringe prior to administering.
5. Koate–HT contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required in patients of blood groups A, B or AB, the possibility of the onset of intravascular haemolysis should be considered.
6. Administration equipment and any reconstituted Koate–HT not used should be discarded.

Warnings

1. Allergic reactions including chills, fever and hypersensitivity reactions, may result from the administration of Factor VIII preparations.
2. When large or frequently repeated doses are required in patients of blood groups A, B or AB, there is a possibility of intravascular haemolysis. Should this condition occur leading to progressive anaemia, administration of serologically compatible type O packed red blood cells should be considered. Also, the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.
3. Massive doses of Factor VIII preparations may result in hyperfibrogenaemia.
4. Koate–HT concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate–HT should be weighed against the medical consequence of withholding it, particularly in persons who have had few previous transfusions of blood or blood products.

PHARMACEUTICAL PRECAUTIONS

Koate–HT should be stored under refrigeration (2 to 8°C). Storage of lyophilised powder at room temperature (up to 25°C) for three months, such as in home treatment situations, may be carried out without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur.

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