DATA SHEET

NAME OF PRODUCT

DRIED FACTOR VIII FRACTION BP (KOATE®)

PRESENTATION

Koate®, is a stable, purified, dried concentrate of human Factor VIII (Antihaemophilic Factor, AHF, AHG) which contains approximately 25-40 times as much Factor VIII as an equal volume of fresh plasma.

Each bottle of Koate contains the labelled amount of anti-haemophilic activity in International Units (IU). One IU is defined by use of the World Health Organisation Standard for Blood Coagulation Factor VIII, human. The final product, when reconstituted as directed, contains 1% Dextrose (anhydrous) USP and is hypertonic. Koate contains anti-A and anti-B blood group isoagglutinins (see discussion under Precautions).

USES

Koate is indicated 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 provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes or in order to perform emergency and elective surgery on haemophiliacs.

Antihaemophilic Factor (Human) is not effective in the treatment of von Willebrand's disease.

DOSAGE, RECONSTITUTION and ADMINISTRATION

Dosage

Each bottle of Koate has the AHF activity in IUs stated on the label of the bottle. One IU is defined by use of the World Health Organisation Standard for Blood Coagulation Factor VIII, human.

Abildgaard et al have reported from studies in haemophilic children a linear dose-response relation with an approximate yield of 2% rise in Factor VIII activity for each unit of Factor VIII per kg of body weight transfused. Clinical experience with Koate has demonstrated an essentially identical dose-response relationship. Therefore, the following formulae provide a guide for dosage calculations:

Expected Factor VIII increase (in % of normal) =

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

IU required = body weight (kg) x desired Factor VIII (% normal) x 0.5

It should be emphasised, however, that all efforts should be made to follow the course of therapy with Factor VIII level assays. 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 to raise the plasma Factor VIII level to 20-30% of normal. If the haemorrhage is moderate or 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 the desired levels.

The above discussion is presented as a reference and a guideline. It should be emphasised that the dosage of Koate required for normalising haemostasis must be individualised according to the needs of the patient. Factors to be considered include the weight of the patient, the severity of the deficiency, the severity of the 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 than would be estimated in order to attain satisfactory clinical results. If the Factor VIII level fails to attain that expected dosage, or if bleeding is not controlled after adequate calculated dosage, the presence of Factor VIII inhibitor should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory procedure. When an inhibitor is present, the dosage requirement for AHF is extremely variable and the dosage can be determined only by the clinical response.

Reconstitution and Administration

1. Warm unopened diluent (Sterile Water for Injection, USP) and Koate to room temperature, but not higher than 37°C (99°F).
2. Remove the plastic flip-top caps from both bottles to expose the central portions of the rubber stoppers and cleanse each stopper with suitable antiseptic immediately before each piercing. We recommend the following procedure: First swab the stopper with Iodine Tincture followed by a sterile antiseptic swab.
3. With a sterile needle and syringe withdraw the appropriate volume of diluent and transfer to the bottle of lyophilized Koate. The Koate bottle is not sealed under vacuum. Add the Sterile Water for Injection, USP diluent gently so as to avoid excessive foaming. Do not bleed out air either before or after reconstitution.
4. Withdraw needle from the concentrate bottle stopper and gently agitate the bottle from time to time until the Koate powder is completely dissolved. Reconstitution usually requires less than 5 minutes.
5. After the concentrate powder is completely dissolved, withdraw the Koate 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.
6. If the same patient is to receive more than one bottle of Koate, the contents of two bottles may be drawn into the same syringe through filter needles before attaching the vein needle. Additional bottles may be drawn into the same syringe through filter needles supplied.

ADVERSE REACTIONS

PHARMACEUTICAL PRECAUTIONS

LEGAL CATEGORY

PACKAGE QUANTITIES

CONTRA INDICATIONS, WARNINGS, ETC.

Contraindications

There are no specific contraindications to the use of Antihaemophilic Factor (Human). (Please read Indications section carefully before use).

Koate concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis virus should be assumed and the hazard of administering Koate concentate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products.

Kasper and Kipnis have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild haemophilia, they recommend single donor products. However, for patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They

believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients.

Precautions

1. Koate is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koate, since no benefit may be expected from its use in treating other causes of haemorrhage.
2. After reconstitution, administer promptly (within 3 hours). Do not refrigerate after reconstitution. NOTE: The recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution. Koate, in the vial unopened, is sterile. It is fully stable, without potency loss for at least 24 hours at room temperature after reconstitution.
3. Administer only by the intravenous route.
4. A filter needle should be used prior to administering.
5. Koate 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 intravascular haemolysis should be considered.
6. Administration equipment and any reconstituted Koate not used should be discarded.

ADVERSE REACTIONS

Allergic reactions may result from the administration of AHF preparations including chills, fever and hypersensitivity reactions.

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. Massive doses may also result in hyperfibrinogenaemia.

The risk of hepatitis is present with the administration of AHF concentrate preparations (see discussion under WARNING).

PHARMACEUTICAL PRECAUTIONS

Koate should be stored under refrigeration (2 to 8°C; 35 to 46°F). Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for six months, such as in home treatment situations, may be done without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur. Reconstituted Koate should not be refrigerated and should be used within three hours of reconstitution.

LEGAL CATEGORY

P.O.M.

PACKAGE QUANTITIES

How Supplied

Koate is supplied in single dose bottles with the total units of Factor VIII activity and total grams of protein stated on the label of each bottle. A suitable volume of Sterile Water for Injection, USP, and a sterile filter needle are provided.

FURTHER INFORMATION

Koate offers many advantages over single-unit cryoprecipitate in replacement therapy of haemophilia patients. Among the most significant are the following:

1. As Koate contains highly purified and concentrated Factor VIII, therapeutic amounts of Factor VIII can be administered in a relatively small volume.
2. Because of the high degree of purity, adequate Factor VIII can be supplied with relatively smaller amounts of fibrinogen and other non-Factor VIII proteins. This is particularly desirable when high circulating levels of Factor VIII must be maintained for prolonged periods, or where inhibitors must be overcome.
3. The high Factor VIII potency in the reconstituted product allows intravenous infusion by direct syringe injection or drip infusion. This facilitates office and home treatment.
4. Factor VIII is very stable as a lyophilized product.
5. Each lot of Koate is assayed and labelled for its Factor VIII content. This permits more precise estimation of the appropriate dose than cryoprecipitate, which may have a variable Factor VIII content.
6. Koate is easily stored and transported.

After infusion of AHF, there is an instantaneous rise in the coagulant level, followed by an initial rapid increase in activity, and then a subsequent much slower rate of decrease in activity. The early rapid phase may represent the time of equilibration 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 AHF. Studies with Koate in haemophiliacs have demonstrated an initial 50% disappearance time of five hours, and a biologic half-life of approximately 13 hours. There were no significant differences between bleeding and non-bleeding patients.

Limited Warranty

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use, and that the risk of hepatitis be carefully weighed before the product is prescribed.

PRODUCT LICENCE No.

PL 1605/0004

NAME AND ADDRESS OF LICENCEE

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Cutter

January 1981.

NAME OF PRODUCT

PRESENTATION

USES

DOSAGE, RECONSTITUTION and ADMINISTRATION