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FACSIMILE
DON'T USE

Antihaemophilic Factor (Human), Factor VIII Concentrate Koāte®

SEE SECTIONS ENTITLED "DESCRIPTION" AND "WARNING" FOR DISCUSSION OF HEPATITIS RISK

DESCRIPTION

Antihaemophilic Factor (Human), Koāte® is a stable, purified, dried concentrate of human Antihaemophilic Factor (Factor VIII, AHF, AHG) intended for use in therapy of classical haemophilia (haemophilia A).

Koāte is purified from the cold insoluble fraction of pooled fresh-frozen plasma by modification and refinements of the methods first described by Hershgold, Pool, and Pappenhagen.[1] Koāte contains highly purified and concentrated Factor VIII. The Factor VIII is 50 to 125 times purified over whole plasma, and when reconstituted as directed, Koāte contains approximately 25-40 times as much Factor VIII as an equal volume of fresh plasma.

Each bottle of Koāte contains the labeled amount of antihaemophilic activity in International Units (IU). One IU, as defined by the World Health Organization Standard for Blood Coagulation Factor VIII, human, is approximately equal to the level of AHF found in 1.0 ml of fresh pooled human plasma. The final product, when reconstituted as directed, contains 1% Dextrose (anhydrous) USP and is hypertonic. Koāte contains anti-A and anti-B blood group isoagglutinins (see discussion under Precautions).

THIS PRODUCT HAS BEEN PREPARED FROM LARGE POOLS OF HUMAN VENOUS PLASMA COLLECTED FROM MANY PAID DONORS. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN FOUND NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HB_sAg) USING A U.S. FEDERALLY APPROVED TEST OF AT LEAST THIRD-GENERATION SENSITIVITY. UNFORTUNATELY, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUSES. SEE WARNING.

NO KNOWN LABORATORY TEST METHOD CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT HEPATITIS.

CLINICAL PHARMACOLOGY

Haemophilia A is a hereditary bleeding disorder characterized by deficient coagulant activity of the specific plasma protein clotting factor, Factor VIII. In afflicted individuals, haemorrhages may occur spontaneously or after only minor trauma, and surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koāte provides an increase in plasma levels of Factor VIII and can temporarily correct the coagulation defect in these patients.

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

1. As Koāte 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 Antihaemophilic Factor (Human), Koāte® is assayed and labelled for its Factor VIII content. This permits a more precise estimation of the appropriate dose than with cryoprecipitate.
6. Koāte is easily stored and transported.

After infusion of AHF, 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.[2,3] 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 halflife of the infused AHF.[3] Studies with Koāte in haemophilic patients have demonstrated an initial 50% disappearance time of five hours, and a biologic halflife of approximately 13 hours.[2] There were no significant differences between bleeding and nonbleeding patients.[2]

INDICATIONS AND USAGE

Koāte 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. Koāte 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.

CONTRAINDICATIONS

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

WARNING

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

Kasper and Kipnis[4] 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 or blood 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. Antihaemophilic Factor (Human), Koāte® is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte, 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. Koāte 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. Koāte 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 Koāte not used should be discarded.

ADVERSE REACTIONS

Allergic reactions may result from the administration of AHF preparations including chills, fever, and hypersensitivity reactions.[5,6]

When large or frequently repeated doses are required in patients of blood groups A, B or AB, there is a possibility of intravascular haemolysis.[7-9] Should this condition occur leading to progressive anaemia, administration of type O packed red blood cells should be considered.[7] Also the administration of type specific cryoprecipitate has been recommended for maintaining adequate Factor VIII levels.[8] Massive doses may also result in hyperfibrinogenaemia.[10]

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

DOSAGE

Each bottle of Koāte has the AHF activity in IUs stated on the label of the bottle.

Abildgaard, et al[11] 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 Koāte has demonstrated an essentially identical dose-response relationship.[12] Therefore, the following formulae provide a guide for dosage calculations:

$$\text{Expected Factor VIII increase (in \% of normal)} = \frac{\text{IU administered} \times 2.0}{\text{body weight (in kg)}}$$

$$\text{IU required} = \text{body weight (kg)} \times \text{desired Factor VIII (\% normal)} \times 0.5$$

It should be emphasized, 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.

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Prophylaxis of spontaneous haemorrhage

The level of Factor VIII required to prevent spontaneous haemorrhage is approximately 5% of normal while a level of 30% of normal is the minimum required for haemostasis following trauma and surgery.[13-15] Mild superficial or early haemorrhages may respond to a single dose of 10 IU/kg of AHF,[12,16] leading to an *in vivo* rise of approximately 20% Factor VIII level. In patients with early haemarthrosis (mild pain, minimal or no swelling, erythema, warmth, and minimal or no joint limitation), if treated promptly, even smaller doses may be adequate.[16-18]

Mild haemorrhage

In cases of minimal haemorrhage, therapy need not be repeated unless there is evidence of further bleeding.

Moderate haemorrhage and minor surgery

For more serious haemorrhages and for minor surgical procedures, the patient's plasma Factor VIII level should be raised to 30-50% of normal for optimum clot formation.[16,19] This usually requires an initial dose of 15-25 IU/kg, and if further therapy is required, a maintenance dose of 10-15 IU/kg every 8-12 hours.

Severe haemorrhage

In patients with life-threatening bleeding, or haemorrhage involving vital structures (central nervous system, retropharyngeal and retroperitoneal spaces, iliopsoas sheath), it may be desirable to raise the Factor VIII level to 80-100% of normal in order to achieve haemostasis.[16,19-21] This may be achieved with an initial AHF dose of 40-50 IU/kg and a maintenance dose of 20-25 IU/kg every 8-12 hours.

Major surgery

For major surgical procedures, Kasper[19] recommends that a dose of AHF sufficient to achieve a level of 80 to 100% of normal be given an hour before the procedure. It is recommended that the Factor VIII level be checked prior to going to surgery to assure the expected level is achieved. A second dose half the size of the priming dose should be given about five hours after the first dose. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10-14 days, depending on the nature of the operative procedure.

The above discussion is presented as a reference and a guideline. It should be emphasized, the dosage of Antihaemophilic Factor (Human), Koāte,® required for normalizing haemostasis must be individualized 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 Koāte 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 Antihaemophilic Factor (Human), Koāte,® 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, USP 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 Koāte. The Koāte 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 Koāte powder is completely dissolved. Reconstitution usually requires less than 5 minutes.
5. After the concentrate powder is completely dissolved, withdraw the Koāte 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 Koāte, 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.

HOW SUPPLIED

Koāte 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 is provided.

STORAGE

Koāte 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 Koāte should not be refrigerated and should be used within three hours of reconstitution.

CAUTION

U.S. Federal law prohibits dispensing without a prescription.

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, the directions be followed carefully during use, and the risk of transmitting hepatitis be carefully weighed before the product is prescribed.

No warranty express or implied, including any warranty of merchantability or fitness, is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labelling, including the package insert, for this product except by printed notice from the Company's Berkeley office. Prescriber and user of this product must accept the terms hereof.

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