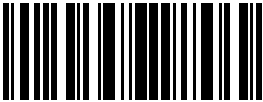


Antihemophilic Factor (Human)

Koāte®-DVI

Double Viral Inactivation
Solvent/Detergent Treated and Heated in Final Container at 80°C



3054838

DESCRIPTION

Antihemophilic Factor (Human), Koāte®-DVI, is a sterile, stable, purified, dried concentrate of human Antihemophilic Factor (AHF, Factor VIII) which has been treated with tri-n-butyl phosphate (TNBP) and polysorbate 80 and heated in lyophilized form in the final container at 80°C for 72 hours. Koāte-DVI is intended for use in therapy of classical hemophilia (hemophilia A).

Koāte-DVI 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-DVI contains purified and concentrated Factor VIII. The Factor VIII is 300–1000 times purified over whole plasma. Part of the fractionation may be performed by another licensed manufacturer. When reconstituted as directed, Koāte-DVI contains approximately 50–150 times as much Factor VIII as an equal volume of fresh plasma. The specific activity, after addition of Albumin (Human), is in the range of 9–22 IU/mg protein. **Koāte-DVI must be administered by the intravenous route.**

Koāte-DVI contains antihemophilic factor 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 Factor VIII found in 1.0 mL of fresh pooled human plasma. The final product when reconstituted as directed contains not more than (NMT) 1500 µg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 µg/mL polysorbate 80, NMT 5 µg/g tri-n-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 µg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL Albumin (Human).

CLINICAL PHARMACOLOGY

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

After infusion of Antihemophilic Factor (Human), there is usually 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.(2-4) 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 Antihemophilic Factor (Human).(3)

The removal and inactivation of spiked relevant and model enveloped and non-enveloped viruses during the manufacturing process for Koāte-DVI have been validated in laboratory studies at Grifols Therapeutics LLC. Studies performed with the model enveloped viruses indicated that the greatest reduction was achieved by TNBP/polysorbate 80 treatment and 80°C heat. For this reason, VSV (Vesicular Stomatitis Virus, model for RNA enveloped viruses) and HIV-1 (Human Immunodeficiency Virus Type 1) were studied only at these two steps of the manufacturing process. The efficacy of the dry heat treatment was studied using all of the viruses, including BVDV (Bovine Viral Diarrheal Virus, model for hepatitis C virus) and Reo (Reovirus Type 3, model for viruses resistant to physical and chemical agents, such as hepatitis A), and the effect of moisture content on the inactivation of HAV (Hepatitis A Virus), PPV (Porcine Parvovirus, model for parvovirus B19), and PRV (Pseudorabies Virus, model for large enveloped DNA viruses) was investigated.

Table 1. Summary of In Vitro Log₁₀ Viral Reduction Studies

	Enveloped Model Viruses				Non-enveloped Model Viruses		
	HIV-1	BVDV	PRV	VSV	Reo	HAV	PPV
Model for	HIV-1/2	HCV	Large enveloped DNA viruses	RNA enveloped viruses	HAV and viruses resistant to chemical and physical agents	HAV	B19
Global Reduction Factor	≥9.4	≥10.3	≥9.3	≥10.9	9.4	≥4.5	3.7

Similar studies have shown that a terminal 80°C heat incubation for 72 hours inactivates non-lipid enveloped viruses such as hepatitis A and canine parvovirus in vitro, as well as lipid enveloped viruses such as hepatitis C.(5-7)

Koāte-DVI is purified by a gel permeation chromatography step serving the dual purpose of reducing the amount of TNBP and polysorbate 80 as well as increasing the purity of the Factor VIII.

A two-stage clinical study using Koāte-DVI was performed in individuals with hemophilia A who had been previously treated with other plasma-derived Factor VIII concentrates. In Stage 1 of the pharmacokinetic study with 19 individuals, statistical comparisons demonstrated that Koāte-DVI is bioequivalent to the unheated product, Koāte®-HP. The incremental in vivo recovery ten minutes after infusion of Koāte-DVI was 1.90% IU/kg (Koāte-HP 1.82% IU/kg). Mean biologic half-life of Koāte-DVI was 16.12 hours (Koāte-HP 16.13 hours). In Stage II of the study, participants received Koāte-DVI treatments for six months on home therapy with a median of 52 days (range 23–94). No evidence of inhibitor formation was observed, either in the clinical study or in the preclinical investigations.(2)

INDICATIONS AND USAGE

Koāte-DVI is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koāte-DVI provides a means of temporarily replacing the missing clotting factor in order to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia.

Koāte-DVI contains naturally occurring von Willebrand factor, which is co-purified as part of the manufacturing process.

Koāte-DVI has not been investigated for efficacy in the treatment of von Willebrand disease, and hence is not approved for such usage.

CONTRAINDICATIONS

None known.

WARNINGS

Koāte-DVI is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. It is emphasized that hepatitis B vaccination is essential for patients with hemophilia and it is recommended that this be done at birth or diagnosis.(8,9) Hepatitis A vaccination is also recommended for hemophilic patients who are hepatitis A seronegative.

PRECAUTIONS

General

- Koāte-DVI is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte-DVI.
- Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
- Administer only by the intravenous route.**
- Filter needle should be used prior to administering.
- Koāte-DVI 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, patients of blood groups A, B, or AB should be monitored by means of hematocrit for signs of progressive anemia, as well as by direct Coombs' tests.
- Product administration and handling of the infusion set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.
Place needles in sharps container after single use. Discard all equipment including any reconstituted Koāte-DVI product in accordance with biohazard procedures.

Pregnancy Category C

Animal reproduction studies have not been conducted with Koāte-DVI. It is also not known whether Koāte-DVI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Koāte-DVI should be given to a pregnant woman only if clearly needed.

Pediatric Use

Koāte-DVI has not been studied in pediatric patients. Koāte-HP, solvent/detergent treated Antihemophilic Factor (Human), has been used extensively in pediatric patients.

Spontaneous adverse event reports with Koāte-HP and Koāte-DVI for pediatric use were within the experience of those reports for adult use.

Information for Patients

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women and immune-compromised individuals.

Symptoms of parvovirus B19 infection include fever, drowsiness, chills and runny nose followed about 2 weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

ADVERSE REACTIONS

Allergic-type reactions may result from the administration of Antihemophilic Factor (Human) preparations.(10,11)

Ten adverse reactions related to 7 infusions were observed during a total of 1053 infusions performed during the clinical study of Koāte-DVI, for a frequency of 0.7% infusions associated with adverse reactions. All reactions were mild and included paraesthesia, vision blurred, headache, nausea, abdominal pain, and feeling jittery.(2)

DOSAGE AND ADMINISTRATION

The reconstituted product must be administered intravenously by either direct syringe injection or drip infusion. The product must be administered within 3 hours after reconstitution.

General Approach to Treatment and Assessment of Treatment Efficacy

The dosages described below are presented as general guidance. It should be emphasized that the dosage of Koāte-DVI required for hemostasis must be individualized according to the needs of the patient, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors, and the Factor VIII level desired. It is often critical to follow the course of therapy with Factor VIII level assays.

The clinical effect of Koāte-DVI is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koāte-DVI than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected Factor VIII levels, or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory tests.

When an inhibitor is present, the dosage requirement for Antihemophilic Factor (Human) is extremely variable and the dosage can be determined only by the clinical response. Some patients with low titer inhibitors (10 Bethesda Units) can be successfully treated with Factor VIII without a resultant anamnestic rise in inhibitor titer.(12) Factor VIII levels and clinical response to treatment must be assessed to insure adequate response. Use of alternative treatment products, such as Factor IX Complex concentrates, Antihemophilic Factor (Porcine) or Anti-Inhibitor Coagulant Complex, may be necessary for patients with high titer inhibitors. Immune tolerance therapy using repeated doses of Factor VIII concentrate administered

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frequently on a predetermined schedule may result in eradication of the Factor VIII inhibitor.(13,14) Most successful regimens have employed high doses of Factor VIII administered at least once daily, but no single dosage regimen has been universally accepted as the most effective. Consultation with a hemophilia expert experienced with the management of immune tolerance regimens is also advisable.

Calculation of Dosage

The in vivo elevation in Factor VIII level (percent of normal) can be estimated by multiplying the dose of Antihemophilic Factor (Human) per kilogram of body weight (IU/kg) by 2%. This method of calculation is based on clinical findings by Abildgaard et al.(15) and is illustrated in the following examples:

Expected % Factor VIII increase (% of normal) =
$$\frac{\text{\# units administered} \times 2\% \text{ /IU/kg}}{\text{body weight (kg)}}$$

Example for a 70 kg adult:
$$\frac{1400 \text{ IU} \times 2\% \text{ /IU/kg}}{70 \text{ kg}} = 40\%$$

or

Dosage required (IU) =
$$\frac{\text{body weight (kg)} \times \text{desired \% Factor VIII increase (\% of normal)}}{2\% \text{ /IU/kg}}$$

Example for a 15 kg child:
$$\frac{15 \text{ kg} \times 100\%}{2\% \text{ /IU/kg}} = 750 \text{ IU required}$$

The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines:

Mild Hemorrhage

Mild superficial or early hemorrhages may respond to a single dose of 10 IU per kg.(4) leading to an in vivo rise of approximately 20% in the Factor VIII level. Therapy need not be repeated unless there is evidence of further bleeding.

Moderate Hemorrhage

For more serious bleeding episodes (e.g., definite hemarthroses, known trauma), the Factor VIII level should be raised to 30%–50% by administering approximately 15 - 25 IU per kg. If further therapy is required, repeated doses of 10 - 15 IU per kg every 8-12 hours may be given.(16)

Severe Hemorrhage

In patients with life-threatening bleeding or possible hemorrhage involving vital structures (e.g., central nervous system, retropharyngeal and retroperitoneal spaces, iliopectas sheath), the Factor VIII level should be raised to 80% - 100% of normal in order to achieve hemostasis. This may be achieved in most patients with an initial Antihemophilic Factor (Human) dose of 40-50 IU per kg and a maintenance dose of 20-25 IU per kg every 8-12 hours.(17,18) For major surgical procedures, Factor VIII levels should be checked throughout the perioperative course to ensure adequate replacement therapy.

Surgery

For major surgical procedures, the Factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. The Factor VIII level should be checked to assure that the expected level is achieved before the patient goes to surgery. In order to maintain hemostatic levels, repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of Factor VIII replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate hemostasis.(17,18)

Prophylaxis

Factor VIII concentrates may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.(19)

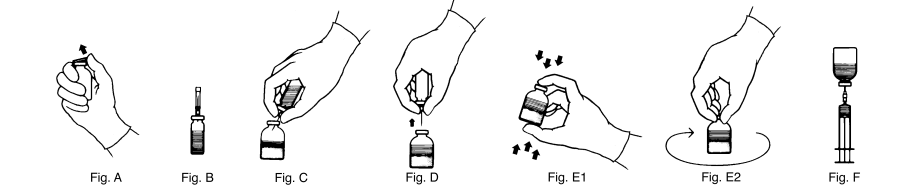
Reconstitution

Vacuum Transfer

Note: Aseptic technique should be carefully followed. All needles and vial tops that will come into contact with the product to be administered via the intravenous route should not come in contact with any non-sterile surface. Any contaminated needles should be discarded by placing in a puncture proof container, and new equipment should be used.

- After removing all items from the box, warm the sterile water (diluent) to room temperature (25°C, 77°F).
- Remove shrink band from product vial. **If the shrink band is absent or shows signs of tampering, do not use the product and notify Grifols Therapeutics LLC immediately.**
- Remove the plastic flip tops from each vial (Fig. A). Cleanse vial tops (grey stoppers) with alcohol swab and allow surface to dry. After cleaning, do not allow anything to touch the latex (rubber) stopper.
- Carefully remove the plastic sheath from the short end of the transfer needle. Insert the exposed needle into the diluent vial to the hub. (Fig. B)
- Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
- Invert the diluent vial and insert the attached needle into the vial of concentrate at a 45° angle (Fig. C). This will direct the stream of diluent against the wall of the concentrate vial and minimize foaming. The vacuum will draw the diluent into the concentrate vial. **
- Remove the diluent bottle and transfer needle (Fig. D).
- Immediately after adding the diluent, agitate vigorously for 10–15 seconds, (Fig. E1) then swirl continuously until completely dissolved (Fig. E2). Some foaming will occur, but attempt to avoid excessive foaming. The vial should then be visually inspected for particulate matter and discoloration prior to administration.
- Clean the top of the vial of reconstituted Antihemophilic Factor (Human), Koâte®-DVI, again with alcohol swab and let surface dry.
- Attach the filter needle (from the package) to a sterile syringe. Withdraw the Koâte-DVI solution into the syringe through the filter needle (Fig. F).
- Remove the filter needle from the syringe and replace with an appropriate injection or butterfly needle for administration. Discard filter needle into a puncture proof container.
- If the same patient is using more than one vial of Koâte-DVI, the contents of multiple vials may be drawn into the same syringe through the filter needles provided.

**If vacuum is lost in the concentrate vial during reconstitution, use a sterile syringe and needle to remove the sterile water from the diluent vial and inject it into the concentrate vial, directing the stream of fluid against the wall of the vial.



Rate of Administration

The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in 5 to 10 minutes is generally well-tolerated.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Koâte-DVI is supplied in a kit containing one single use vial of Koâte-DVI lyophilized powder, one vial of Sterile Water for Injection, USP, one sterile double-ended transfer needle, one sterile filter needle, and one sterile administration set.

Approximate Factor VIII Activity	Diluent
250 IU	5 mL
500 IU	5 mL
1000 IU	10 mL

STORAGE

Koâte-DVI should be stored under refrigeration (2–8°C; 36–46°F). Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 6 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.

Rx only

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