Full Prescribing Information

1 KOĀTE-DVI

Factor VIII (Human)
250/500/1000 IU/vial

For intravenous use after reconstitution only.

2 THERAPEUTIC INDICATIONS

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.

Limitation of Use

KOĀTE-DVI is not indicated for the treatment of von Willebrand disease.

3 DOSAGE AND ADMINISTRATION

Each bottle of KOĀTE-DVI has the Factor VIII content in international units per bottle stated on the label of the bottle. 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.[1] 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 frequently on a predetermined schedule may result in eradication of the Factor VIII inhibitor.[2,3] 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 percent 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,[4] and is illustrated in the following examples:

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

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

or

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

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,[5] 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.[6]

Severe Hemorrhage

In patients with life-threatening bleeding or possible hemorrhage involving vital structures (e.g., central nervous system, retropharyngeal and retroperitoneal spaces, iliopsoas 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.[7,8] 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.[8,9]

Prophylaxis

Factor VIII concentrates may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.[9]

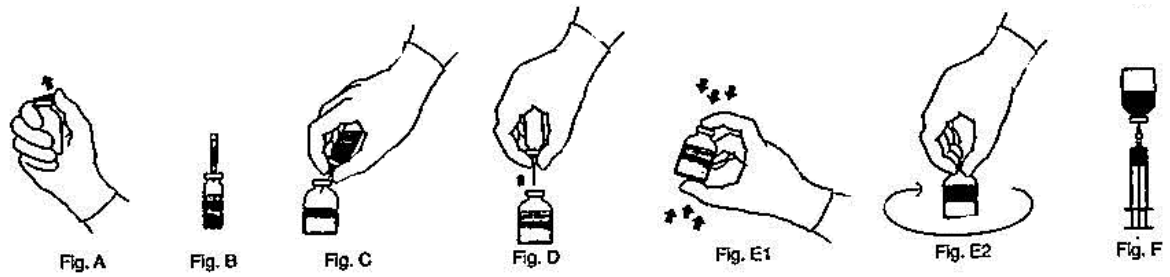
Reconstitution

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.

1. After removing all items from the box, warm the sterile water (diluent) to room temperature (25˚C, 77˚F).
2. 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.
3. Remove the plastic flip tops from each vial (Fig. A). Clean vial tops (grey stoppers) with alcohol swab and allow surface to dry. After cleaning, do not allow anything to touch the latex (rubber) stopper.
4. 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)
5. Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
6. 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.**
7. Remove the diluent bottle and transfer needle (Fig. D).
8. 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.
9. Clean the top of the vial of reconstituted KOĀTE-DVI again with alcohol swab and let surface dry.
10. Attach the filter needle (from the package) to a sterile syringe. Withdraw the KOĀTE-DVI solution into the syringe through the filter needle (Fig. F).
11. 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.
12. If the same patient is using more than one vial of KOĀTE-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.

4 DOSAGE FORMS AND STRENGTHS

KOĀTE-DVI is available as a lyophilized powder for reconstitution in single-use vials of 250, 500 and 1,000 IU of Factor VIII activity. The actual Factor VIII potency is labeled on each KOĀTE-DVI vial.

5 CONTRAINDICATIONS

Hypersensitivity, including anaphylaxis, to the active substance or to any of the excipients listed in section 9 *(Description).*

6 WARNINGS AND PRECAUTIONS

6.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible. Early signs of hypersensitivity reactions, which can progress to anaphylaxis, may include angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea. If hypersensitivity symptoms occur, discontinue use of the product immediately and administer appropriate emergency treatment.

6.2 Neutralizing Antibodies

The formation of neutralizing antibodies (inhibitors) to Factor VIII may occur. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained, or if

bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. *[see Warnings and Precautions (6.5)]*

6.3 Intravascular Hemolysis

KOĀTE-DVI (Antihemophilic Factor [Human]) contains blood group isoagglutinins which are not clinically significant when small doses are used to treat minor bleeding episodes. However, when large and/or frequent doses of KOĀTE-DVI are given to patients with blood groups A, B, or AB, acute hemolytic anemia may occur, resulting in increased bleeding tendency or hyperfibrinogenemia. Monitor these patients for signs of intravascular hemolysis and falling hematocrit. *[see Warnings and Precautions (6.5)]* Should this condition occur, leading to progressive hemolytic anemia, discontinue KOĀTE-DVI and consider administering serologically compatible Type O red blood cells and providing alternative therapy.

6.4 Transmissible Infectious Agents

Because KOÃTE-DVI is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses**,** the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in the product**.** The risk that the product will transmit viruses 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 removing certain viruses during manufacture. Despite these measures, this product may still potentially transmit diseases.

6.5 Monitoring: Laboratory Tests

- Monitor for intravascular hemolysis and decreasing hematocrit values in patients with A, B or AB blood groups who are receiving large or frequent doses of KOĀTE-DVI.

7 ADVERSE REACTIONS

The most common adverse drug reactions (frequency ≥ 5 % of subjects) observed in the clinical trial were nervousness, headache, abdominal pain, nausea, paresthesia and blurred vision.

7.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The safety assessment of KOĀTE-DVI is based on data from a 2-stage, safety, pharmacokinetic (PK) and efficacy clinical trial in which twenty subjects with severe hemophilia A (<1% endogenous Factor VIII activity) were evaluable for safety. Nineteen subjects were enrolled in Stage I of the trial, including 15 Caucasian, 3 Hispanic, and 1 Black subjects. The mean age was 29 years (range: 13.9 – 46.4 years). Nineteen subjects, including the 18 subjects who completed Stage I, and one new subject were enrolled in Stage II. The mean age was 30 years (range: 13.9 – 46.4). The subjects received a total of 1053 infusions. Ten adverse reactions related to 7 infusions were reported in 4 subjects. These were: nervousness (2 subjects [10%]), headache (1 subject [5%]), abdominal pain (1 subject [5%]), nausea (1 subject [5%]), paresthesia (1 subject [5%]), and blurred vision (1 subject [5%]).

Immunogenicity

Subjects were monitored for neutralizing antibodies (inhibitors) to Factor VIII by the Bethesda assay at baseline and at 8, 17 and 26 weeks. No evidence of inhibitor formation was observed in the clinical trial.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to KOĀTE-DVI in the study described above with the incidence of antibodies in other studies or to other products.

7.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

- Blood and Lymphatic System Disorders: Factor VIII inhibition, hemolytic anemia
- Immune System Disorders: Hypersensitivity including anaphylaxis, rash, pruritus

- Injury, Poisoning and Procedural Complications: Post-procedural hemorrhage
- Nervous System Disorders: Generalized clonic-tonic seizure

7.3 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

Additionally, you can also report to www.perrigo-pharma.co.il.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with KOĀTE-DVI use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using KOĀTE-DVI. It is 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KOĀTE-DVI in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KOĀTE-DVI and any potential adverse effects on the breast-fed infant from KOĀTE-DVI or from the underlying maternal condition.

8.3 Pediatric Use

Safety and efficacy studies have been performed in 20 previously treated pediatric patients aged 2.5 to 16 years. Subjects received 208 infusions of KOĀTE-DVI for treatment or control of bleeding episodes, including perioperative management, and routine prophylaxis.

Children have shorter half-life and lower recovery of Factor VIII than adults. Because clearance of Factor VIII (based on per kilogram body weight) is higher in children, higher or more frequent dosing may be needed.

8.4 Geriatric Use

Clinical studies of KOĀTE-DVI did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. Individualize dose selection for geriatric patients.

9 DESCRIPTION

KOĀTE-DVI, Antihemophilic Factor (Human), is a sterile, stable, dried concentrate of human antihemophilic factor in lyophilized powder form for reconstitution for intravenous injection. The product is supplied in single-use vials containing nominally 250, 500, or 1,000 international units (IU or units). Each vial of KOĀTE-DVI is labeled with the actual amount of Factor VIII expressed in IU. One IU is defined by the current World Health Organization International Standard for Factor VIII concentrate, which can be traced to the level of Factor VIII found in 1 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 human albumin.

List of excipients: sodium chloride, human albumin, L-histidine, calcium chloride.

Solvent for reconstitution: water for injection.

KOĀTE-DVI is purified from the cold insoluble fraction of pooled human plasma; the manufacturing process includes solvent/detergent (TNBP and polysorbate 80) treatment and heat treatment of the lyophilized final container. A gel permeation chromatography step serves the dual purpose of reducing the amount of TNBP and polysorbate 80 as well as increasing the purity of the Factor VIII in KOĀTE-DVI to 300 to 1,000 times over whole plasma. When reconstituted as directed, KOĀTE-DVI contains approximately 50 to 150 times as much Factor VIII as an equal volume of fresh plasma.

The specific activity after addition of human albumin is in the range of 9 to 22 IU/mg protein. KOĀTE-DVI also contains naturally occurring von Willebrand factor, which is co-purified as part of the manufacturing process.

The KOĀTE-DVI manufacturing process includes two dedicated steps with virus inactivation capacity. The solvent/detergent treatment step has the capacity to inactivate

enveloped viruses (such as HIV, HCV, HBV, and WNV). Heat treatment at 80ºC for 72 hours has the capacity to inactivate enveloped viruses (such as HIV and HCV) as well as non-enveloped viruses (such as HAV and B19V). The polyethylene glycol (PEG) precipitation/depth filtration step has the capacity to remove both enveloped and non-enveloped viruses. The accumulated virus reduction factors for KOĀTE-DVI manufacturing process are presented in Table 1.

Table 1: Virus Clearance Capacity (Log_{10}) for the Antihemophilic Factor (Human) Manufacturing Process

	Enveloped Viruses					**Non-enveloped Viruses**		
	HIV-1	**BVDV**	**PRV**	**VSV**	**WNV**	**Reo3**	**HAV**	**PPV**
Model for	HIV-1/2	HCV	Large enveloped DNA viruses (e.g., herpes virus)	Enveloped RNA viruses	WNV	Non-enveloped viruses	HAV	B19V
Global Reduction Factor	≥ 12.0	≥ 11.5	≥ 10.8	≥ 10.9	≥ 5.9*	≥ 9.9	≥ 5.5	4.8

* WNV inactivation was evaluated only for the solvent/detergent treatment step

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents. The manufacturing process has been shown to decrease TSE infectivity of that experimental model agent (a total of 5.1 log_{10} reduction), providing reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

KOĀTE-DVI temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis.

10.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation Factor VIII, resulting in a prolonged plasma clotting time as measured by the activated partial thromboplastin time (aPTT) assay. Treatment with KOĀTE-DVI normalizes the aPTT over the effective dosing period.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of KOĀTE-DVI were evaluated in a prospective, two-stage clinical trial of 20 previously treated patients (PTPs) with severe hemophilia A. In Stage I, the PK parameters for 19 subjects were based on plasma Factor VIII activity after a single intravenous infusion of 50 IU/kg of KOĀTE-DVI. Bioequivalence of the dry heat-treated KOĀTE-DVI to the unheated KOĀTE was demonstrated by comparison of C_{max} and the area under the curve, AUC_{0-48} (Table 2). The incremental *in vivo* recovery ten minutes after infusion of dry heat-treated KOĀTE-DVI was 1.90% unit/kg (unheated KOĀTE was 1.82% units/kg). Mean biologic half-life was 16.1 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 to 94 days). At the end of 6 months, the mean AUC_{0-48} was 1471 ± 237 unit*hour/100 mL, the C_{max} was 99 ± 13 unit/100 mL, and the $t_{1/2}$ was 16 ± 3.9 hours.

Table 2: PK Parameters of KOĀTE-DVI (Stage I of Crossover Trial)

Parameter	KOĀTE-DVI Dry Heat-treated (mean ± SD)	KOĀTE Unheated (mean ± SD)
AUC_{0-48} (IU·hr/mL)	1432 ± 288	1477 ± 343
C_{max} (IU/mL)	103 ± 19	99 ± 20
T_{max} (hr)	0.41 ± 0.26	0.43 ± 0.44
Half life (hr)	16.1 ± 3.2	16.1 ± 5.1

11 CLINICAL STUDIES

The efficacy of KOĀTE-DVI for the treatment of bleeding episodes was demonstrated in a 2-stage, safety, PK and efficacy clinical trial. Stage I was a randomized, single-blind, single-dose, crossover, and PK study comparing heat-treated KOĀTE-DVI with unheated KOĀTE. Nineteen subjects were randomized and received a single dose of 50 IU/kg of either heated KOĀTE-DVI or unheated KOĀTE for PK assessment. Stage II was a 6 month open-label safety study conducted at two hemophilia centers. Nineteen subjects received KOĀTE-DVI, including for on-demand treatment and control of bleeding episodes. The study populations included 15 Caucasians, 3 Hispanic, and 1 Black subjects. A total of 306 bleeding episodes were treated, of which 82% were treated with a single infusion of Factor VIII.

12 REFERENCES

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13 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KOĀTE-DVI is supplied in single-use vials containing 250, 500 or 1,000 IU of Factor VIII activity, packaged with 5 mL or 10 mL of Sterile Water for Injection, one sterile double-ended transfer needle, one sterile filter needle, and one sterile administration set. The actual amount of KOĀTE-DVI in IU is stated on each carton and vial label.

Components used in the packaging of KOĀTE-DVI are not made with natural rubber latex.

Storage and Handling

- Store the KOĀTE-DVI package at 2 to 8°C. Do not freeze.

- KOĀTE-DVI may also be stored at room temperature (up to 25°C) for up to 6 months.
- Do not use after the expiration date.
  The expiry date of the product is indicated on the packaging materials.
- Use reconstituted KOĀTE-DVI immediately or within 3 hours of reconstitution.

14 MANUFACTURER:

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15 REGISTRATION HOLDER:

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