

## **Prescribing Information**

### **Koate<sup>®</sup>-DVI 250/500/1000**

Factor VIII (Human)

250/500/1000 IU/vial

Powder for solution for injection

For intravenous use after reconstitution only.

#### **1 THERAPEUTIC INDICATIONS**

Koate-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.

Koate-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.

#### **2 DOSAGE AND ADMINISTRATION**

Each vial of Koate-DVI is labeled with the actual Factor VIII potency in international units (IU). 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 Koate-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 Koate-DVI is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koate-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.<sup>1</sup> 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.<sup>2,3</sup> 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,<sup>4</sup> and is illustrated in the following examples:

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

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

or

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

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

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,<sup>5</sup> 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.<sup>6</sup>

#### 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.<sup>7,8</sup> For major surgical procedures, Factor VIII levels should be checked throughout the perioperative course to ensure adequate replacement therapy.

## **Surgery**

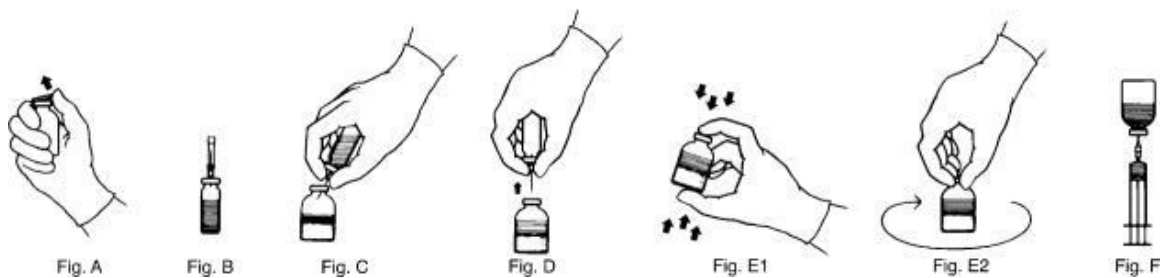
For major surgical procedures, the factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. The factor VIII level should be checked to assure that the expected level is achieved before the patient goes to surgery. In order to maintain hemostatic levels, repeat 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.<sup>8,9</sup>

## **Prophylaxis**

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

### **2.1 Preparation and Reconstitution**

1. Use aseptic technique (clean and sanitized) and a flat work surface during the reconstitution procedure.
2. Bring the vials of Koate-DVI and the diluent (Sterile Water for Injection) to room temperature before use.
3. Remove shrink band from the Koate-DVI vial. Do not use Koate-DVI if the shrink band is absent or shows signs of tampering.
4. Remove the plastic cap from the Koate-DVI vial (Fig. A) and clean the top of the stopper with an alcohol swab. Allow the stopper to dry.
5. Repeat this step with the vial of sterile water.
6. Carefully remove the plastic sheath from the short end of the transfer needle and insert the exposed needle into the diluent vial to the hub. (Fig. B)
7. Place the Koate-DVI vial upright on a flat surface. Remove the sheath from the other end of the transfer needle.
8. While holding the Koate-DVI vial securely on a flat surface, insert the needle into the vial at a 45° angle to minimize foaming (Fig. C). The vacuum will draw the diluent into the concentrate vial. If vacuum is lost, use a sterile syringe and needle to remove the sterile water from the diluent vial and inject it into the Koate-DVI vial, directing the stream of fluid against the wall of the vial.
9. Remove the diluent vial and transfer needle (Fig. D).
10. Agitate vigorously for 10-15 seconds, (Fig. E1) then swirl continuously until completely dissolved (Fig. E2). Avoid excessive foaming. The reconstituted solution should be clear to opalescent. Do not use if particulate matter and discoloration are observed.
11. Clean the top of the vial of reconstituted Koate-DVI with alcohol swab and let surface dry.
12. Attach the filter needle (from the package) to a sterile syringe. Withdraw the Koate-DVI solution into the syringe through the filter needle (Fig. F).
13. Remove the filter needle from the syringe and discard the filter needle into a puncture proof container. Use Koate-DVI within 3 hours after reconstitution. Do not refrigerate after reconstitution.



## 2.2 Administration

### For intravenous administration only

- If the dose requires more than one vial of Koate-DVI:
  - Reconstitute each vial using a new transfer needle.
  - Draw up all the solution into a single syringe.
- Visually inspect the final solution for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.
- Attach the syringe to the connector end of an infusion set.
- Administer intravenously. The rate of administration should be determined by the patient's comfort level, and no faster than 10 mL per minute.

## 3 DOSAGE FORMS AND STRENGTHS

Koate-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 Koate-DVI vial.

## 4 CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylaxis, to the active substance or to any of the excipients listed in section 11 (*Description*).

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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.

### 5.2 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 \(5.5\)](#)]

### **5.3 Intravascular Hemolysis**

Koate-DVI 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 Koate-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 \(5.5\)](#)] Should this condition occur, leading to progressive hemolytic anemia, discontinue Koate-DVI and consider administering serologically compatible Type O red blood cells and providing alternative therapy.

### **5.4 Transmissible Infectious Agents**

Because Koate-DVI is made from human blood, 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.

Report all infections suspected by a physician possibly to have been transmitted by this product.

### **5.5 Monitoring: Laboratory Tests**

- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of Koate-DVI. Use Bethesda Units (BU) to report inhibitor levels.
- 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 Koate-DVI.

## **6 ADVERSE REACTIONS**

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

### **6.1 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 Koate-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 Koate-DVI in the study described above with the incidence of antibodies in other studies or to other products.

## **6.2 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

## **6.3 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 Padagis via the following address: [Padagis.co.il](https://padagis.co.il)

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

### Risk Summary

There are no data with Koate-DVI use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using Koate-DVI. It is not known whether

Koate-DVI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Koate-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 Koate-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 Koate-DVI and any potential adverse effects on the breast-fed infant from Koate-DVI or from the underlying maternal condition.

## **8.4 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 Koate-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.

## **8.5 Geriatric Use**

Clinical studies of Koate-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.

## **11 DESCRIPTION**

Koate-DVI, Antihemophilic Factor (Human), is a sterile, stable, dried concentrate of human antihemophilic factor in lyophilized white to pale yellow 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 Koate-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.

Koate-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 Koate-DVI to 300 to 1,000 times over whole plasma. When reconstituted as directed, Koate-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. Koate-DVI also contains naturally occurring von Willebrand factor, which is co-purified as part of the manufacturing process.

The Koate-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 80°C 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 Koate-DVI manufacturing process are presented in [Table 1](#).

**Table 1: Virus Clearance Capacity (Log<sub>10</sub>) 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

<sup>1</sup> \* WNV inactivation was evaluated only for the solvent/detergent treatment step

Additionally, the Koate-DVI 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<sub>10</sub> reduction), providing reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 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 Koate-DVI normalizes the aPTT over the effective dosing period.



### 12.3 Pharmacokinetics

The pharmacokinetics (PK) of Koate-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 Koate-DVI. Bioequivalence of the dry heat-treated Koate-DVI to the unheated Koate 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 Koate-DVI was 1.90% unit/kg (unheated Koate was 1.82% units/kg). Mean biologic half-life was 16.1 hours.

In Stage II of the study, participants received Koate-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  $1471 \pm 237$  unit\*hour/100 mL, the  $C_{max}$  was  $99 \pm 13$  unit/100 mL, and the  $t_{1/2}$  was  $16 \pm 3.9$  hours.

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

Parameter	Koate-DVI Dry Heat-treated (mean $\pm$ SD)	Koate Unheated (mean $\pm$ SD)
$AUC_{0-48}$ (IU·hr/mL)	1432 $\pm$ 288	1477 $\pm$ 343
$C_{max}$ (IU/mL)	103 $\pm$ 19	99 $\pm$ 20
$T_{max}$ (hr)	0.41 $\pm$ 0.26	0.43 $\pm$ 0.44
Half life (hr)	<b>12.4</b> <u>16.1 <math>\pm</math> 3.2</u>	<b>12.5</b> <u>16.1 <math>\pm</math> 5.1</u>

## 14 CLINICAL STUDIES

The efficacy of Koate-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 Koate-DVI with unheated Koate-DVI. Nineteen subjects were randomized and received a single dose of 50 IU/kg of either heated Koate-DVI or unheated Koate-DVI for PK assessment. Stage II was a 6 month open-label safety study conducted at two hemophilia centers. Nineteen subjects received Koate-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.

## 15 REFERENCES

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## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### How Supplied

Koate-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 Koate-DVI in IU is stated on each carton and vial label.

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

### Storage and Handling

- Store Koate-DVI in its original package to protect it from light.
- Store the Koate-DVI package at 2 to 8°C. Do not freeze.
- Koate-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.

### Storage after reconstitution

- Use reconstituted Koate-DVI immediately or within 3 hours of reconstitution.

## **17 MANUFACTURER**

**Grifols Therapeutics LLC**  
North Carolina 27709, USA

## **18 REGISTRATION HOLDER**

Padagis Israel Agencies Ltd.  
1 Rakefet St., Shoham.

## **19 REGISTRATION NUMBERS**

Koate-DVI 250: 117-88-29924

Koate-DVI 500: 117-89-29930

Koate-DVI 1000: 117-90-29931

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