GRIFOLS

Koate-DVI

Antihemophilic Factor VIII (Human) 250 IU / 5 mL

1 INDICATIONS AND USAGE

Koate®-DVI is a human plasma-derived antihemophilic factor indicated for the control and prevention of bleeding episodes or in order to perform emergency and elective surgery in patients with hemophilia A (hereditary Factor VIII deficiency).

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- Dose and duration of treatment depend on the severity of the Factor VIII deficiency, location and extent of bleeding, and the patient's clinical condition.
- Koate-DVI contains antihemophilic factor activity in international units (IU). Calculation of the required dose of Factor VIII is based on the empirical finding that one IU of Factor VIII per kg body weight raises the plasma Factor VIII activity by approximately 2% of normal activity or 2 IU/dL.

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- The required dose can be determined using the following formula:

Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (% normal or IU/dL) x 0.5

- Estimate the expected *in vivo* peak increase in Factor VIII level, expressed as IU/dL (or % normal), using the following formula:

Estimated Increment of Factor VIII
(% normal or IU/dL) = [Total Dose (IU)/Body Weight (kg)] x 2

- Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses. Base the dose and frequency on the individual clinical response.

Control and Prevention of Bleeding Episodes

A guide for dosing Koate-DVI for the control and prevention of bleeding episodes (1,2) is provided in Table 1. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 1: Dosage Guidelines for Patients with Hemophilia A

Type of Bleeding	Factor VIII:C Level Required (% of normal)	Doses (IU/kg)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor Large bruises Significant cuts or scrapes Uncomplicated joint hemorrhage	30	15	12 (twice daily)	Until hemorrhage stops and healing has been achieved (1–2 days).
Moderate Nose, mouth and gum bleeds Dental extractions Hematuria	50	25	12 (twice daily)	Until healing has been achieved (2–7 days, on average).
Major Joint hemorrhage Muscle hemorrhage Major trauma Hematuria Intracranial and intraperitoneal bleeding	80-100	Initial: 40-50 Maintenance: 25	12 (twice daily)	For at least 3–5 days Until healing has been achieved for up to 10 days. Intracranial hemorrhage may require prophylaxis therapy for up to 6 months.
Surgery	Prior to surgery: 80-100 After surgery: 60-100	40-50 30-50	Once 12 (twice daily)	Prior to surgery For the next 7–10 days, or until healing has been achieved.

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 VIII (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. Factor VIII levels and clinical response to treatment must be assessed to insure adequate response. 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. 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.

Prophylaxis

For long term prophylaxis against bleeding in patients with severe hemophilia A, the usual doses are 10 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

2.2 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 the 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, 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 is 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.

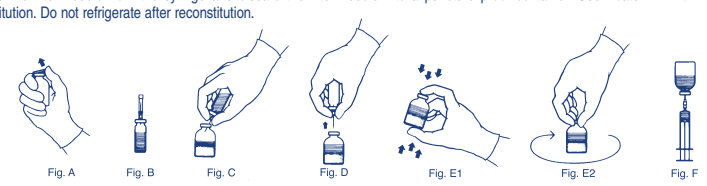

Fig. A Fig. B Fig. C Fig. D Fig. E1 Fig. E2 Fig. F

2.3 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.

2.4 Incompatibilities

Koate-DVI must not be mixed with other medicinal products.

3 DOSAGE FORMS AND STRENGTHS

Koate-DVI is available as a lyophilized powder for reconstitution in a single-use vial of 250 IU of Factor VIII activity.

4 CONTRAINDICATIONS

Koate-DVI is contraindicated in patients who have had hypersensitivity reactions, including anaphylaxis, to Koate-DVI or its components. *[see Description (11)]*

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

Koate-DVI is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the donor population and selection of individual donors by a medical interview; (2) screening of individual donations and plasma pools for viral infection markers; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

5.5 Monitoring: Laboratory Tests

- Monitor plasma Factor VIII activity levels by performing a validated test (e.g., one-stage clotting assay) to confirm that adequate Factor VIII levels have been achieved and maintained. *[see Dosage and Administration (2.1)]*
- 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.

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6 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.

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

The reactions which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to Koate-DVI, or a combination of these factors, are:

- 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

You may report any side effects of adverse drug reactions directly to the National Centre for Adverse Drug Reactions Monitoring by calling Tel. 03-78835490, or visiting the website npra.gov.my *[Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)]*

7 INTERACTIONS WITH OTHER MEDICAMENTS

No interactions of human coagulation Factor VIII products with other medicinal products have been reported.

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.

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

Koate-DVI has not been studied in pediatric patients. The unheated, solvent/detergent treated Koate had been used extensively in pediatric patients.

Spontaneous adverse event reports with the unheated product and Koate-DVI for pediatric use were within the experience of those reports for adult use.

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.

10 OVERDOSAGE

No symptoms of overdose with human coagulation Factor VIII have been reported.

11 DESCRIPTION

Koate-DVI, Antihemophilic Factor VIII (Human), is a sterile, stable, dried concentrate of human antihemophilic factor VIII in lyophilized powder form for reconstitution for intravenous injection. The product is supplied in a single-use vial containing nominally 250 international units (IU or units). 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.

Koate-DVI is purified from the cold insoluble fraction of pooled fresh-frozen plasma. Koate-DVI is purified by a gel permeation chromatography step serving the purpose of increasing the purity of the Factor VIII and simultaneously reducing the amount of tri-n-butyl phosphate (TNBP) and polysorbate 80 employed at the previous Solvent/Detergent treatment, a procedure with virus inactivation capacity. Koate-DVI contains purified and concentrated Factor VIII. The Factor VIII is 300 to 1,000 times purified over whole plasma. Koate-DVI is heated in lyophilized form in the final container at 80°C for 72 hours, as a second manufacturing step with virus inactivation capacity. 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 Albumin (Human), is in the range of 9–22 IU/mg protein. Koate-DVI also contains naturally occurring von Willebrand factor, because human coagulation factor VIII and von Willebrand factor are present in plasma as a complex of the two proteins and are co-purified as part of the manufacturing process. Koate-DVI contains not less than (NLT) 250 IU naturally occurring von Willebrand factor in the 250 IU presentation.

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 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 clearance capacity for Koate-DVI manufacturing process is presented in Table 2.

Table 2: 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 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_{10} 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 3). 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 ± 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 3: PK Parameters of Koate-DVI (Stage I of Crossover Trial)

Parameter	Koate-DVI Dry Heat-treated (mean ± SD)	Koate 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

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. Nineteen subjects were randomized and received a single dose of 50 IU/kg of either heated Koate-DVI or unheated Koate 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

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19(1):e1-47.

2. Abildgaard CF. Current concepts in the management of hemophilia. Semin Hematol 1975;12(3):223-32.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Koate-DVI is supplied in a single-use vial containing 250 IU of Factor VIII activity, packaged with 5 mL of Sterile Water for Injection, one sterile double-ended transfer needle, one sterile filter needle, and one sterile administration set.

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

Strength	Volume	Registration Number
250 IU	5 mL	MAL19890637ARZ

Storage and Handling

- Store Koate-DVI in its original package to protect it from light.
- Store refrigerated at 2 to 8°C and no more than 6 months at room temperature (up to 25°C) at any time prior to the expiration date. Avoid freezing.
- Do not use after the expiration date.
- Use reconstituted Koate-DVI immediately or within 3 hours of reconstitution.
- Discard any unused product or waste material in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

- Inform patients to immediately report the following early signs and symptoms of hypersensitivity reactions to their healthcare professional: angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea. *[see Warnings and Precautions (5.1)]*
- Inform patients that the development of inhibitors to Factor VIII is a possible complication of treatment with Koate-DVI. Advise the patients to contact their healthcare provider for further treatment and/or assessment if they experience a lack of clinical response to Koate-DVI because this may be a manifestation of an inhibitor. *[see Warnings and Precautions (5.2)]*
- Inform patients that Koate-DVI is made from human plasma and may carry a risk of transmitting infectious agents. While the risk that Koate-DVI can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by incorporating manufacturing steps with virus clearance capacity, patients should report any symptoms that concern them. *[see Warnings and Precautions (5.4)]*

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